USE OF COMPLEX TONES IN THE ASSESSMENT OF AUDITORY CORTICAL FUNCTION IN PATIENTS UNDERGOING SURGERY FOR TEMPORAL LOBE EPILEPSY

by

MARIA DA ASSUNÇÃO MORAIS E CUNHA VAZ PATO, M.D., M.Sc.

INSTITUTE OF NEUROLOGY

UNIVERSITY COLLEGE LONDON

A thesis submitted as partial fulfillment of the requirements for the degree of Doctor of Philosophy in Clinical Studies, University of London

ProQuest LLC
789 East Eisenhower Parkway
P.O. Box 1346
Ann Arbor, MI 48106-1346

Acknowledgements

I am greatly indebted to Dr. Stephen J. Jones for his ever-present guidance, friendly advice and careful supervision throughout this study and the writing of the present thesis. I would also like to thank him for his encouragement and support during my stay in London.

I would like to thank all patients and volunteers who freely gave their time, and without whom this work would ever be possible.

I am also indebted to Dr. Pamela Thompson for her help and advice with the patient's neuropsychological data that she kindly supplied. My thanks also go to Dr Louis Lemieux for his help and guidance as well as the permission to use the patient's MRI results obtained at Chalfont.

I would also like to thank the help provided by Dr. Alexandra Lázaro with her comments on the statistical analysis of the data.

I am very grateful to all the persons working in the Telemetry Unit of the National Hospital for Neurology and Neurosurgery – consultants, technicians and nurses - for their permission to see their patients and for all the practical help during the recording of the data.

An additional word of gratitude goes to all my colleagues, nurses, secretaries and technicians of the Department of Clinical Neurophysiology at the National Hospital for Neurology and Neurosurgery who never tired of sharing great moments with me, and who helped to make my stay in London a great time.

I would like to thank Professor J.B.Keating and Professor C.Oliveira, who started it all.

Finally, last but not the least, I would like to thank Luis, Martim and Bernardo for their support, care and love during this journey, which was crucial to see it ended.

Abstract

Previous reports described three types of auditory evoked potentials (AEP) obtained with continuous synthesized musical instrument tones, two generated in the supratemporal cortex, a third one in the lateral temporal cortex, more prominently on the right. The objective of this work was to examine those AEP in a patient population undergoing surgery for temporal lobe epilepsy, which may direct or indirectly affect their generators.

A group of 31 normal subjects and 148 epileptic patients were evaluated with AEPs to onset of tones, changes in their spectral and changes in their spectro-temporal patterns. Patients were divided according to their clinical and magnetic resonance imaging (MRI) characteristics: 43 had right hippocampal sclerosis (HS), 55 had left HS, 35 had lesions that were not HS, 15 had complex partial epilepsy with normal MRI. Forty-two patients with HS or other cerebral lesions were selected for surgery and were re-evaluated 3-6 months post surgery.

In the pre surgical evaluation, the incidence of AEP abnormalities was 90 to 100%. Post surgically, the incidence of abnormalities did not differ significantly from pre surgical ones. Serial AEP assessment revealed deterioration and improvement in comparable numbers of cases.

Correlation tests were performed between AEP surgical evolution and neuropsychological surgical evolution. Some correlations were observed to the right HS subgroup, but the pattern did not clearly suggest a common cause for any deficit. No correlations were seen for the left HS subgroup. No significant correlation was seen between surgical volume of removed tissue and AEP changes for any patient group.

In conclusion, no evidence was found for any deleterious effect of surgery on the AEPs. The high incidence of pre surgical abnormalities may point to a generalized mild dysfunction of auditory cortical processes in this group of patients.

Table of contents

List of figures

List of tables

Introduction

CHAPTER 1.1 Basic neuroanatomy and electrophysiology of the auditory pathways

1.1.1 -The peripheral auditory system

The advancing sound front enters the external auditory canal directly striking the tympanic membrane. The middle ear processes the transfer of the vibration from the comparatively large, low impedance tympanic membrane to the much smaller and higher impedance oval window, via the sequential formation of ossicles- the *malleus*, the *uncus* and the *stapes*. The ossicle activity is dependent on two muscles, the *stapedius* and the *tensor tympani*, both apparently responding to loud sound and to sound produced by bodily movements. A band pass filtering is proposed to occur in the middle ear – its elastic stiffness (related with the tympanic membrane and the ossicle ligaments, as well as the compression and expansion of the air in the cavity) attenuates sounds at low frequencies (Pickles, 1982, a). High frequency stimuli break up the vibration pattern of the tympanic membrane into separate zones, reducing the effectiveness of transmission (Khanna and Tonndorf, 1972). The middle ear seems to act as a modulator of sound, improving its transmission and reducing the amount of reflected sound, also modulating the quality of sound entering the inner ear.

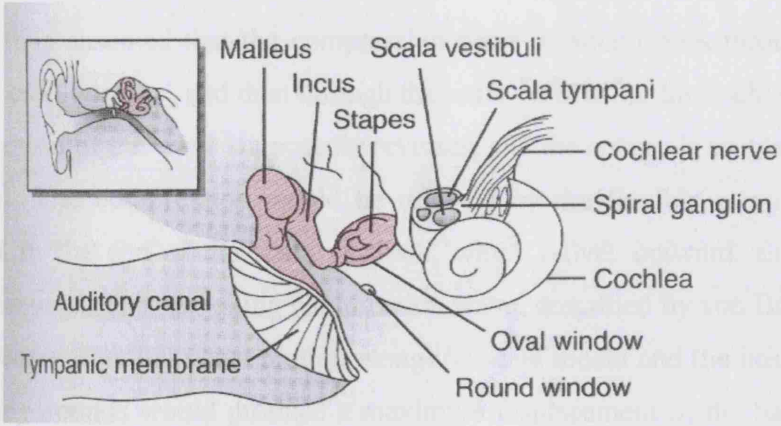

Fig. 1-1.Anatomy of the middle ear (adapted from Guyton and Hall, 10th ed.)

From the oval window inward, the sound pathway is in fluid filled spaces. The inner ear is embedded deep in the temporal bone, mostly containing perilymph. Its main component is the *cochlea,* a coiled bony system with two extremities - the base, which is narrow and stiff, and the apex, which is wider and more compliant. The cochlea is composed of three compartments filled with fluid, which run its length: two of them, the *scala timpani* and the *scala vestibuli* communicate via the *helicotrema* (a small aperture at the apical end of the cochlea). The *scala media* form an intermediate compartment of the cochlea filled with endolymph, which is not in direct communication with the other two compartments, and contains the *basilar membrane*.

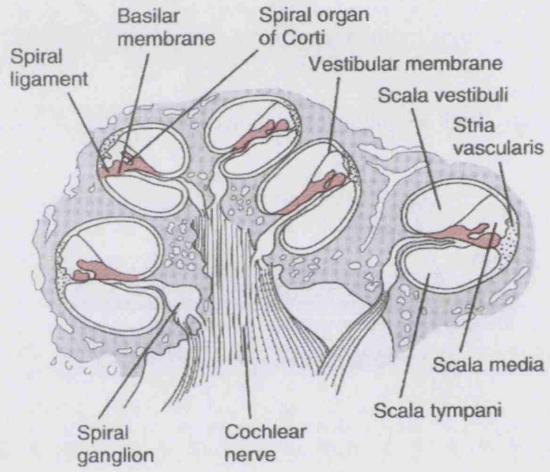

Fig.1-2. Anatomy of the cochlea (adapted from Guyton and Hall, 10th ed.)

It is assumed that the compression wave of sound goes through the ossicle chain and the oval window, and then through the scala vestibuli to the cochlea apex. At this point, the direction of the wave supposedly reverses, and the energy is sent back through the scala tympani. The compression would be relieved by the flexible *round window* membrane situated in the end of the scala vestibuli, which moves outward, as the stapes footplate moves inward. This travelling compression wave, described by von Békésy in 1960, would send a corresponding wave motion along the scala media and the basilar membrane. High frequency sounds would produce a maximum displacement of the basilar membrane near the oval window, while low frequency sounds would produce a displacement of the basilar membrane near the apex (rev. Pickles, 1982, b).

The basilar membrane holds the organ of Corti, often referred to as the end organ of hearing. The organ of Corti is formed by support cells and mostly by the hair cells, outer and inner hair cells. The inner hair cells are responsible for the detection of the basilar membrane vibration and the excitation of most afferent fibres in the auditory nerve, being connected via the basal end to the peripheral branches of axons of bipolar neurons. The outer hair cells also receive innervation from the auditory nerve, but with less specificity.

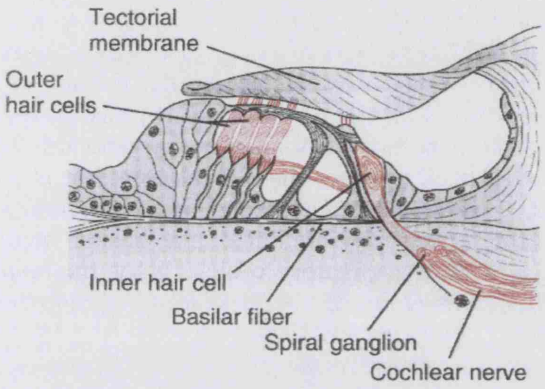

Fig.1-3. Inner and outer hair cells in the basilar membrane (adapted from Guyton and Hall, 10th ed.)

Both types of cells receive efferent connections from higher centres that modulate their intrinsic responses. While the inner hair cells work mainly as transducers of the basilar membrane movements, the outer hair cells are active elements that increase the vibration amplitude of the basilar membrane. Indirectly, the outer hair cells affect the behaviour of all the hair cells as well as their frequency selectivity, mainly at low intensities (rev. Møller, 2000, a).

The tonotopicity and the oscillatory movements of the basilar membrane are able to code the different frequencies of the sound. Each point in the basilar membrane is supposed to have a certain centre frequency (characteristic frequency) and bandwidth and slopes defining the limits of the band pass. These *"filters"* are relatively narrow along the basilar membrane to low intensity sounds, but show increasing bandwidths towards high intensity sounds, implying a coarser absolute frequency resolution for high intensities of sound. To a pure tone of a certain frequency the basilar membrane presents peak amplitude of movement in a specific location, related to the specific frequency of the sound: hair cells located in the area whose frequency corresponds to the maximal stimulus are the most excited ones. Movements of the cilia (through ion channels) will polarize or depolarize the

cell according to the different directions they assume. This will cause release of neurotransmitters and repeated firing of axons in the auditory nerve (rev. Pickles, 1982, c; Kelly, 1991).

The basilar membrane is believed to work as kind of a partial Fourier analyzer, a parallel series of narrow band pass filters through which the acoustic signal is passed. The main role of the basilar membrane seems to be to divide sounds into different spectral bands before the information is processed. This will allow the temporal information in different frequency bands to be coded independently and with more ease, and also allows the spectral information to be place encoded (rev. Moore, 1997; Møller, 2000, c).

1.1.2 -The auditory pathways

Throughout the auditory system, nerve fibres are arranged in an orderly fashion preserving the relationship between sound frequency and cochlear place. Responses of the auditory nerve fibres convey information about all the attributes of the sound stimulus. Individual nerve fibres also act as band pass filters, with a spectral selectivity resulting from the basilar membrane place they innervate. Their firing activity can signal onset and offset of sound, the presence of continuous tones and also convey messages of the temporal regularity of the sound (rev. by Møller, 2000, b). Each frequency element of a complex sound has its periodicity encoded by different populations of nerve fibres, with spectral and temporal features still linked and transmitted together. After a Fourier-like transformation, the frequency selectivity of the tuning curve of an auditory fibre determined by a complex sound seems to be identical to the one determined by pure tones (Goblick and Pffeiffer, 1969).

The auditory nervous system is highly complex, possessing ascending and descending components. The ascending pathways comprise the *classical auditory pathway*, projecting from the cochlear nucleus to the *superior olivary complex*, the central nucleus of the contralateral inferior colliculus and the lateral portion of the ventral division of the contralateral *medial geniculate body* of the thalamus and then to the auditory cortex.

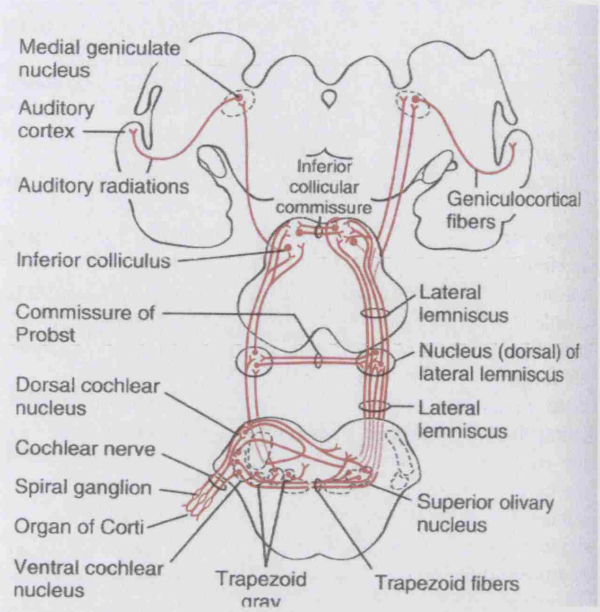

Fig.1-4. Illustration of the auditory pathways (adapted from Guyton and Hall, 10th ed.)

A second pathway, ***the non-classical pathway***, which branches off at the level of the inferior colliculus or before, has two divisions, the polysensory and the diffuse system. *The diffuse system* projects to the secondary auditory cortex and the reticular nucleus of the thalamus, while the *polysensory system* projects to the anterior auditory cortical field, with collaterals to the reticular nucleus of the thalamus and to the limbic system.

1.1.3 -The cochlear nucleus

The tonotopical organization is maintained in the cochlear nucleus of the cat and isofrequency bands have been described in the monkey with high frequencies situated dorsally and low frequencies situated ventrally (rev. Webster and Garey, 1990). Tone bursts triggered onset responses, sustained responses and offset responses in different populations of neurons in the cochlear nucleus. The structure of the dorsal cochlear nucleus appears to be more complex than the structure of the ventral cochlear nucleus, and its most prominent feature is its laminar organization. Neurons from the dorsal cochlear nucleus act in a network of feed back and inhibitory-excitatory impulses signalling silence and sound of high intensities (rev: Gulick et al., 1989, a). Other patterns of the presentation of sound (absence of onset response with a build up of activity slowly; the presence of individual responses to individual sound frequencies; cells continuously firing for the duration of the sound) are also seen and thought to help the encoding of complex sounds. Suppression

effects from lateral inhibition are seen, stronger than in the auditory nerve, leading to the strong emphasis of certain parts of the sound pattern (Greenwood and Goldberg, 1970).

Some cochlear nuclei cells of the cat may have a central excitatory frequency range with an inhibitory external area, while other cells respond to broadband noise more convincingly (Young and Brownell, 1976). Stimuli varying in time, such as tones swept in frequency or intensity and frequency modulated tones produce more vigorous responses in some cells of the dorsal cochlear nucleus. It is possible that phase related and intensity features are treated in the ventral cochlear nucleus, while time and spectral analysis is probably resolved in the dorsal cochlear nucleus (eg: Britt and Starr, 1976, Møller, 1978).

The temporal precision of transmission of a simple or a complex tone seems to increase as a result of synaptic transmission at the cochlear nucleus. To be accurate, the system must evaluate the interval between nerve impulses time locked to individual sound waves. Animal experiments suggested that axons of different lengths may serve as the delaying part of the system and it is postulated that these axons may be located in the cochlear nucleus. A coincidence detector would be located in the superior olivary complex (rev. by Møller, 2000, b), but other structures show similar behaviour like the inferior colliculus in cats (Langner and Schreiner, 1988).

1.1.4 -The superior olivary complex

From the ventral cochlear nuclei arises a major tract, *the trapezoid body.* Fibres from the trapezoid body decussate to the contralateral side and either end in the superior olivary complex or bypass the superior olivary complex to reach the inferior colliculus. This pathway is safe, short in length and preserves many features of the auditory response (rev: Pickles, 1982, d; Gulick et al., 1989, b). A minority of fibres remains ipsilateral, following the same direction.

The dorsal cochlear nucleus originates two tracts: a) *the tract of Monakow or striae acousticae*, which cross to the contralateral nuclei of the *lateral lemniscus* and inferior colliculus, resulting in parallel bilateral representation to the inferior colliculus; b) the *intermediate stria*, which supplies bilaterally nuclei around the *lateral superior olive* and the *medial superior olive* and to a lesser extent, *the lateral lemniscus*. The later pathway is believed to convey information for the analysis of complex sounds, which is mixed with the information on spatial location in the superior olivary complex.

The superior olivary complex receives terminals ranged to allow the coding of binaural time and intensity differences, thereby being an important centre of spatial sound localization. This structure is composed of several nuclei: the largest, known as the lateral superior olivary nucleus receives input from both ears, with the ipsilateral input being excitatory and the contralateral input inhibitory. Neurons in this nucleus respond mainly to interaural sound intensity disparities, an important factor by which sound is localized in the horizontal plane. Cells' characteristic frequencies in the lateral superior olivary nucleus are thought to be arranged tonotopically, favouring high frequency sounds (rev: Pickles, 1982, d; Gulick et al., 1989, a, b). Neurons in the medial superior olivary nucleus respond to disparities in interaural timing, also coding the direction of sound in space and mostly responsive to low frequencies. A third nucleus- the medial nucleus of the trapezoid body- is also arranged tonotopically. Here, neurons present a wide variety of responses to sound frequencies and intensities, with side band, or centre band inhibition or both together and a large number of responses to sound onset.

1.1.5 -The inferior colliculus and the medial geniculate body

The inferior colliculus receives input from the cochlear nuclei contralaterally and from the olivary complex bilaterally, apparently combining the spatial information from the olivary complex with the results of the spectral information from the dorsal cochlear nucleus. The fibres to the inferior colliculus run in the lateral lemniscus tract and some send collaterals to the lateral lemniscus nuclei. The central nucleus of the inferior colliculus is the main auditory relay and sheets of cells with some tonotopic organization form it; low frequencies are found in dorsal sheets, while high frequencies are found in ventral ones. A considerable segregation of function seems to occur in these isofrequency sheets, with bands of time-sensitive binaural neurons separated by bands of intensity-sensitive neurons (Semple and Aitkin, 1979). Complex excitatory and inhibitory interactions are also present with responses varying with intensity and sensitivity to sounds with a specific direction or speed (rev: Pickles, 1982, d).

At the inferior colliculus, the auditory pathway projects both ipsi- and contra-laterally. The contralateral pathway crosses the commissure of the inferior colliculus to the contralateral inferior colliculus and medial geniculate body. The brachium of the inferior colliculus is the ipsilateral pathway to the medial geniculate body of the thalamus and contains auditory fibres from different origins: inferior colliculus, lateral lemniscus and

superior olivary complex. From the inferior colliculus a pathway transmitting auditory spatial information is directed to the superior colliculus (rev. Cohen, 1999).

The system in the thalamus seems to be broadly tuned for frequency and sharply tuned for interaural timing disparities, indicating the optimization for location of one, or at most, a few sources at a time (Fitzpatrick et al., 1997). The medial geniculate body is the specific thalamic relay of the auditory system, receiving afferents from the inferior colliculus and projecting to the auditory cortex. It contains three major divisions: the ventral, medial and dorsal nuclei. The ventral nucleus also has a laminar structure formed by isofrequency sheets of cells, presenting a tonotopic organization with high frequencies localized medially and low frequencies laterally. Ventral nucleus neurons have sharply tuned response areas, selective responses to time and intensity interaural differences, with responses to sound differing in the broadness of their tuning curves while other cells only fire in response to complex sounds and not to pure tones. They project to the primary (AI) and to secondary (AII) auditory cortical regions and posterior ectosylvian gyrus areas in the cat (rev. Gulick et al., 1989, b).

Most of the units in the medial and dorsal divisions of the medial geniculate body are unresponsive to sound, and the ones which show a long latency response with broad tuning curves are located in the medial division. While the medial division projects to the primary auditory cortex, the dorsal division projects to the association auditory cortex.

CHAPTER 1.2 Basic anatomy and electrophysiology of the auditory cortex: animal studies

1.2.1 -Anatomic and cytoarchitectonic divisions

Woolsey and Walzl in 1942 identified two areas responding in a different way to cochlear stimulation in the cat auditory cortex: the *primary auditory cortex (*AI), located in the central ectosylvian gyrus, and the *secundary auditory cortex* (AII), contiguous to AI and located in the ectosylvian gyrus and also in part of the pseudosylvian gyrus. With cytoarchitectonic studies, Rose in 1949 described a third auditory area in the posterior ectosylvian gyrus, later subdivided into posterior and ventroposterior auditory areas.

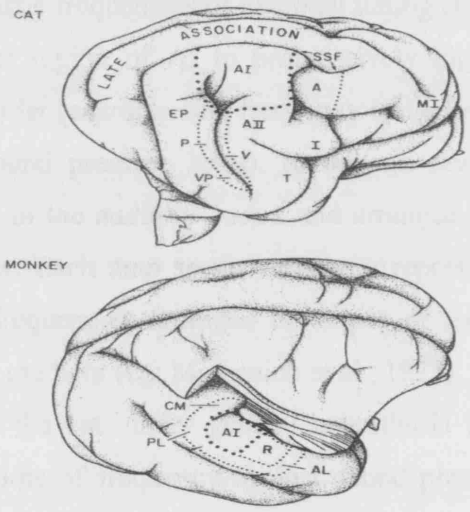

Fig.1-5.Auditory cortical fields in cat and monkey based on electrophysiological studies (adapted from Brugge and Reale, 1985)

Primates and humans have an auditory cortex difficult to access, mostly hidden in the fissure of Sylvius, located in the supratemporal plane. In the monkey, AI and the rostral field are centrally located, surrounded by the caudomedial, posterolateral and anterolateral fields (rev. Pickles, 1982, e; Webster and Garey, 1990).

A common type of cellular organization of the auditory cortex is described in primates: a central region of koniocortex (so called due to the specific granular pattern of layer IV) denominated the *core* is located in AI and some adjacent areas of AII (in the monkey, AI and rostral area). A narrow band of cortex, *the belt,* with features in

intermediate position between the cortex and distant regions, surrounds this area. Further away, *the parabelt* region is a large zone of cortex in the dorsal surface of the *Superior Temporal Gyrus* (rev. Brugge and Reale, 1985; Webster and Garey, 1990). Hackett et al. (1998) described the existence of 2-3 core areas and several belt and parabelt areas in the monkey. Caudal and rostral areas of the parabelt seem to be related and connected between themselves as well as to similar areas of the belt and of the superior temporal gyrus, superior temporal sulcus and the prefrontal cortex (see also Kaas and Hackett, 1998).

1.2.2 -Responses of cortical neurons to pure tones

Extensive single and multiple unit studies in the cat (eg: Reale and Imig, 1980; Merzenich et al., 1975) showed a fairly cochleotopical representation in the primary auditory cortex along its caudal/rostral dimension. This is expressed as an increase in the characteristic frequencies of neuronal tuning curves, from low *characteristic frequencies* in the caudal region of AI to progressively higher characteristic frequencies towards the rostral border (characteristic frequency is the frequency to which the neurons respond to the lowest sound pressure level). In the cat several different cochlear representations are described in the auditory cortex and arranged in a way that they act as mirror images of each other. Each map seems to have a representation of the cochlea with the individual optimal frequencies arranged in stripes or isofrequency lines and perpendicular to the tonotopic gradient (eg: Merzenich et al., 1975).

In the cat, under general anaesthesia the majority of AI neurons exhibit tuning curves (plots of frequency against sound pressure level thresholds) that are narrow and "V"-shaped, sometimes broad or with multiple tips, presumably reflecting convergence of input from several sharply tuned elements. This spectral sensitivity range shows the peripheral dependence on intensity also observed for the basilar membrane. Hence, the narrowest frequency range at threshold intensity varies from a few semitones (one semitone approximately equal to 6% in frequency terms) to many octaves (one octave equal to 100%) for high levels of intensity. Due to this fact, the distribution of cortical activity in response to a pure tone would change with different sound levels. At threshold level, the isofrequency area expected is activated, but with the increase in intensity a spreading of activity via the dorsal and ventral region is observed (Phillips et al., 1994, Schreiner, 1998). Different patterns of response to pure sounds are also present - on, off and on-off responses- with the same units showing different responses for different frequencies of

stimulation (eg: Merzenich and Brugge, 1973). Secondary auditory areas show a poor degree of tonotopicity, with cells in the same area presenting a wide range of characteristic frequencies to threshold stimulation, sometimes so broad that an optimal frequency is not definable.

Recent studies of the auditory cortex revealed non uniform and spatially superimposed functions distributed along the isofrequency lines for different characteristics: response threshold, the dynamic range and shape of response level functions, the bandwidth and shape of frequency response profiles, sensitivity to frequency modulated sounds and binaural interaction as well as sound location coding (rev. Schreiner, 1998 (in the cat), King and Schnupp, 1998). Some of these properties such as sharpness of tuning and response strength to broadband signals may co-vary. It is suggested that neurons in different places represent different combinations of at least these basic attributes and probably several others (Shamma et al., 1993). The use of pure sounds varying in only one characteristic does not seem to be able to reflect the multiple function and networking of which the auditory cells are capable.

1.2.3 -Complex sound processing

The transition from the use of pure tones to complex stimuli in auditory research often resulted in more effective neuronal responses (eg: Whitfield and Evans, 1965; Manley and Muller Preuss, 1978). Cortical neurons seem to respond more effectively to more natural sounds than pure tones. Using reverse correlation techniques in the owl monkey, de Charms et al. (1998) showed that only a minority of neurons in AI presented a simple selectivity for a particular frequency. A large number of cells had multipartite receptive fields, with increased and decreased firing rates related to the temporal structure and spectral contents of the acoustic stimuli, as well as selectivity to direction and velocity of stimulus movement. In the cat, Schreiner and Urbas (1988) described band pass modulation transfer functions in cortical neurons to amplitude modulated sounds. Nelken et al. (1999) demonstrated synchronized activity between AI and the insula for the encoding of amplitude modulated and frequency modulated sounds. Bieser and Muller Preuss (1996) described the neuronal response to amplitude modulated sounds centred on the best modulation frequency of the cortical cells in the squirrel monkey. Both the best modulation frequency and the spectral sensitivity of the cells also seem able to influence the encoding of periodic frequency modulated elements.

In AI stimulus features are probably coded based on the relative spike tuning of each neuron and coordination of relative firing of a network of neurons, so that the effects can summate and become more robust. For frequency modulated sounds, neural encoding takes place by phase encoding to frequency modulated sweeps. However, while phase locking is very prominent in the auditory nerve, central structures seem less responsive to the modulations of sound, suggesting that other mechanisms may be involved (rev. Møller, 2000, d). Bieser (1998) evaluating cortical neurons of the squirrel monkey showed a marked reduction of phase locking at 16Hz repetition rates, and an influence of the best modulation frequency on the quality of periodic encoding. AI and the insula were activated by low modulation rates, while the rostral field was activated by high modulation rates when compared to AI and the insula. Complex sounds, where amplitude and frequency modulations occur together, evoked stronger neuronal responses than the amplitude modulated sounds or frequency modulated sounds in isolation. Cortical neurons also show selectivity for the spatial location of sounds. Middlebrooks (2000) suggested a model where auditory cortical neurons would respond over a broad range of sound locations, the temporal difference between spikes of discharge coding for specific azimuth changes. Units would have a broad tuning for spatial location - they would code panoramically and they would combine information from interaural cues and spectral cues. Sound location would not be determined by a specific anatomically localized population of neurons, but would depend on cellular networks, changing in location and response with different variables such as sound level.

The concept of segregation of functions to different areas of the auditory cortex (eg: Steinschneider et al., 1998; Rauschecker et al., 1995; Kaas and Hackett, 1998), has been complemented by the suggestion that the processing of sound has to include the encoding of different modulated parts of the spectrum. The peaks of the overall spectral envelope and the fine frequency spectra would be organized in parallel areas, with the full auditory perception resulting from a concerted *multiscale representation of* the sound (Shamma, 2000). Studies with ripple analysis techniques provide foundation to multi scale representation of the sound, involving tonotopicity, scale and phase. This system accounts for changes in one of these parameters not greatly affecting the perception of the final message, but it does not totally explain the behaviour of all AI cells- some having non linear and erratic responses to sound. As for sound location, a multiple dimension activity of the auditory cells seems to imply treatment of sound via cellular networks with varying

plasticity. The multi scale representation would imply a parallel representation of different aspects of the same sound object and may represent an advantage in filtering sounds from background noise or in grouping sounds originating from the same source.

1.2.4 -Lesional studies

The real function of the auditory cortex was questioned when it was shown that bilateral lesions of the auditory cortex in cats affected only very slightly the absolute thresholds and the differential intensity thresholds for behavioural identification of sound. Simple frequency discrimination was spared after cortical lesions in monkeys and frequency and intensity discrimination was normal in cats after bilateral ablation of AI, posterior ectosylvian areas and AII. The ablation of the auditory cortex in the monkey seems to produce difficulty in relating the previous tone to the subsequent one or translating this into response terms or both, while deficits in sound location seem more profound than in cats (rev. Webster and Garey, 1990). After bilateral lesions of the auditory cortex, cats were responding to all auditory stimuli, previously defined as positive or negative, in an equal way. A role in the selection of relevant versus irrelevant stimuli was suggested on the basis of these observations (rev: Pickles, 1987, e).

Cortical lesions may be seen as upsetting difficult tasks whilst preserving easier ones, such that the cortex may be perceived as being responsible for organizing the stimuli in order to help their understanding. The analysis of complex sounds is then upset after cortical lesions. With bilateral lesions, cats apparently lost the capacity to recognize the missing fundamental of a harmonic complex (Whitfield, 1980). However, an extensive bilateral ablation of the auditory cortex did not destroy the animals' ability to distinguish a rising from a falling glide (Kelly and Whitfield, 1971). Although not evident due to contralateral and ipsilateral representations, unilateral lesions also produce deficits. In dogs, a unilateral lesion of the auditory cortex resulted in a loss of sensitivity to short tones (10 ms) in the opposite ear. This also happens in monkeys, while sensitivity to longer tones is preserved, suggesting a difficulty with the time dimension of the auditory stimulus (rev. Pickles, 1987, e).

Since the earlier studies of the auditory cortex it is known that multiple representations of the sound are present in the human auditory cortex, meaning that a given point in the cochlea will project to several different points in the cortex. Since the discrimination of spectral features is preserved after cortical lesions, the auditory cortex

must have a more complex objective than the simple discrimination of differences between sounds of different frequencies. Lesions produce losses more related with perception of similarities than differences, and an alternative interpretation of the cortex's function is to group together sounds with a common origin (sound "objects") (Whitfield, 1985). In fact, and in spite of the different lesions described, it is not possible to locate a loss of a skill to a lesion in a small portion of cortex. The whole concept of the auditory cortex as a map with defined areas for different tasks is then anatomically challenged as well. The concept of the cortex as a generator of sound objects, related to its ability to form *"concepts concerning constancies such as the constancy of the position of a sound source when the listener moves, or the constancy of pitch when the harmonic composition changes"* (Whitfield, 1985) would be in agreement with the multiple representation of features as in the models of Shamma (2000) and Middlebrooks (2000) - the neural transformation at each of these levels closely determining the way the concept is formed.

CHAPTER 1.3 The human auditory cortex

1.3.1 -Anatomical studies

In 1909 Brodman described three areas associated with auditory processing in the cerebral cortex within the superior temporal regions (the supratemporal plane). Area 41 receives input from the ventral subdivisions of the medial geniculate body and is located in the posteromedial part of the transverse temporal gyrus on the superior surface of the temporal lobe (also called Heschl's gyrus). Macroscopically, Heschl's gyrus is single and longer in the left hemisphere, with a larger *planum temporale* (known as area 42-TB of von Economo) that extends from the most posterior aspect of the Heschl's gyrus to the end of the Sylvian fissure and that surrounds area 41 posterolaterally. Several anatomic variations have been described for both right and left Heschl's gyrus in humans (eg: Penhune et al., 1996; Leonard et al., 1998). The rostral area, (the temporal pole, area 38) is a special region because of its cytoarchitectonic similarities with the prefrontal cortex and lack of direct thalamic afferents. Its functional role is not defined (rev. Creutzfeldt, 1995). The secondary auditory areas are contiguous: *area 42* continues both anteriorly and laterally in relation to Heschl's gyrus, while *areas 21, 22 and 20* in man coincide reasonably with the superior (Brodman area 22), the middle (Brodman area 21) and the inferior (Brodman area 20) temporal gyrus.

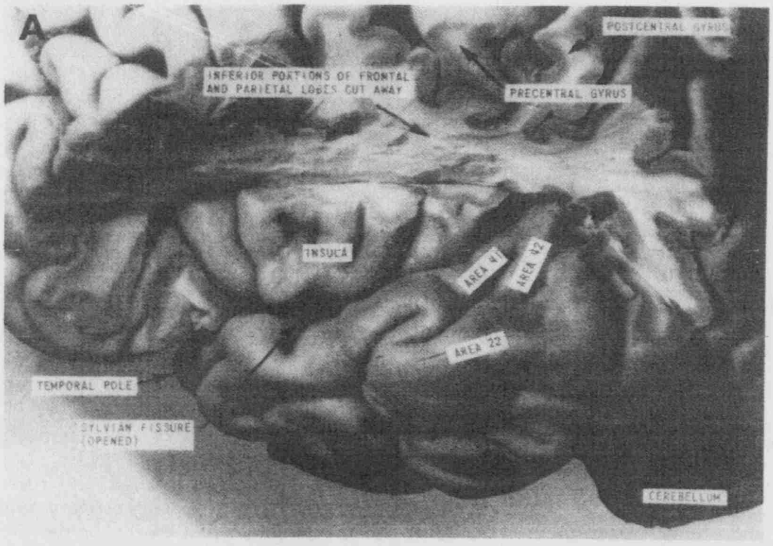

Fig.1-6 An human cortex opened in order to show areas 41, 42 and 22 (adapted from Webster and Garey, 1990)

There is a general agreement that in humans the primary auditory cortex (AI) is located deeply within Heschl´s gyrus. Cytoarchitectonically, von Economo and Horn in 1930 located the primary auditory cortex in the medial half of either the first or the first and part of the second gyrus.

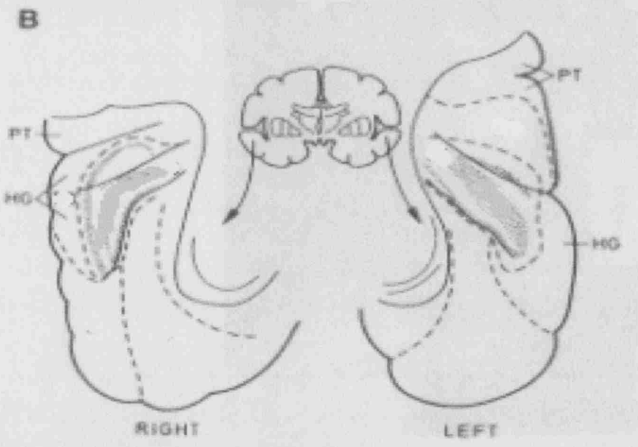

Fig.1-7- The human auditory cortex, showing Heschl´s gyrus on the right and on the left Heschl´s gyrus and the planum temporale (adapted from Webster and Garey, 1990)

In 1980 Galaburda and Sanides demonstrated that the primary auditory cortex was confined to the central two thirds of the single gyrus. In 1993 Rademacher located AI in a single gyrus, but when two gyri were present, AI would be located in the more anterior one

and also in the anterior portion of the gyrus if in the presence of a sulcus intermedius. Following previous primate classification AI would correspond to the core area (in humans, area 41 and part of area 42) while AII would correspond to area 42 and area 22, also corresponding to the belt and parabelt regions (rev. Leonard et al., 1998).

Recent studies of the supratemporal cortex in human cadavers defined 8 distinct cortical areas responding to cytochrome oxidase and acetylcholinesterase staining, using the cytoarchitectonic descriptions of von Economo and Koskinas. Five areas were located in the supratemporal plane (Heschl's gyrus, the planum polare anterior to Heschl's gyrus, the area posterior to Heschl's gyrus, on the posterior convexity of the superior temporal gyrus and on the posterior superior insula); two areas were located laterally and medially to Heschl's gyrus and two areas were located on the insula (Rivier and Clarke, 1997). A detailed study of the primary auditory areas revealed radial and tangential staining differences, compatible with orthogonal strips of functionally differentiated neurons (Clarke and Rivier, 1998).

Advances in surgical techniques and recording procedures allowed access to the auditory cortex, namely in patients undergoing epilepsy surgery. These studies showed different responses to stimuli from different areas. For instance, in 1963 Penfield obtained speech hallucinations stimulating the regions around Heschl's gyrus and the association areas and obtaining simple acoustic sensations from Heschl's gyrus stimulation which were rarely lateralized. In 1987 Creutzfeldt directly stimulated Heschl's gyrus, producing acoustic sensations that were perceived in the contralateral ear. Weak electrical stimuli in the association fields produced no sensation, but a strong stimulus in area 22 produced sound perception, rarely words or speech (rev. Creutzfeldt, 1995). Although a networking solution remains possible at cellular level for the decodification of sound, macroscopically some areas present more affinity to decoding specific sounds than other areas.

1.3.2 -Intracerebral electrophysiological studies

The study of the auditory cortex in humans at the cellular level is obviously restricted. A microelectrode intracellular study of the temporal regions to be excised in epileptic patients recognized the tonotopicity of the human auditory cortex to pure tone stimulation, with high frequencies located more medioposteriorly, and low frequencies located more anteriorly and laterally (Howard et al., 1996). Chatrian et al. (1960) using click trains with high and low rates of stimuli demonstrated that direct neuronal responses

were not confined to the posterior part of the superior temporal gyrus, but also involved the insula. While low rates of stimuli evoked a specific response, an increase in the rate to 15Hz produced a change in the recorded discharges, more complex, with on, driving and off responses from the neurons.

Creutzfeldt et al. (1989, a, b) and Creutzfeldt and Ogemann (1989) evaluated the lateral temporal cortex of epileptic pre-surgical patients with microelectrodes, comparing speech and musical tones. All cells in both hemispheres were driven by speech sounds, with speech being more efficient at inducing responses than pure tones. Neuronal responses were more enthusiastic when the patient paid attention to the stimulus. Neurons on the superior temporal gyrus bilaterally responded to speech with well-defined activation, but with little response to noises or tones, while the medial temporal gyrus and the inferior temporal gyrus were only slightly affected by speech, and not specifically affected by other sounds. Music produced both excitation and inhibition bilaterally (with no differences between the superior, middle and inferior temporal gyri) and with no obvious lateralization, with some neurons showing regular firing for rhythmic stimulation. The authors concluded that the superior temporal gyrus may reflect some general phonetic function of speech while the middle and inferior temporal gyri would only be involved non-specifically in speech perception.

Rademacher et al. (1993) used multicontact subdural recording electrodes implanted on the surface of the superior temporal gyrus in patients undergoing temporal lobe surgery; in a smaller group of patients the electrodes were implanted over Heschl's gyrus. The simultaneous recording from Heschl's gyrus and the superior temporal gyrus gave evidence of two functionally separated areas, Heschl's gyrus apparently providing a short latency input for the superior temporal gyrus. The stimulation of the superior temporal gyrus produced similar situations as described by Penfield in 1963- auditory perceptions like whizzing and jet engines- and also alteration in the perception of sounds in the environment. Click trains evoked responses confined to the posterolateral superior temporal gyrus but the response of this area to single clicks or tones was poor compared with the primary field. According to Rademacher et al. (1993), Heschl's gyrus would contain the primary cortex (or core). The posterolateral superior temporal gyrus would be the auditory parabelt, also receiving projections from Heschl's gyrus and probably being engaged in further processing of sound sequences with very long temporal intervals (see also Howard et al., 2000).

1.3.3 -Lesional studies in humans

Due to the bilateral representation, the lesion-based approach to understanding the auditory cortex is difficult. Unilateral lesions of the human auditory cortex have been reported to produce impairment in the perception of audio verbal material to the contralateral ear, a loss of sensitivity to short tones and also difficulties in perceiving temporal patterns of auditory stimuli. They also produce slight disturbances of cortical localization (rev. Creutzfeldt, 1995). Speech can still be understood when the left temporal auditory cortex is destroyed in isolation and the right auditory cortex is still intact. Based on four patients presenting unilateral lesions on the left cortex with different degrees of deficits in recognition of environmental sounds and in the localization and auditory motion perception, Clarke et al. (2000) suggested two distinct cortical pathways for analyzing auditory stimulus: one lateral, related to auditory recognition, involving the lateral auditory areas and the temporal convexity, and another medial and posterior and related to spatial processing, involving the posterior auditory areas, the insula and the parietal convexity.

Bilateral lesions of the human auditory cortex are rare: they seem to affect the discrimination of time sequences and patterns and even the discrimination of tone duration. Three different clinical syndromes are seen secondary to bilateral temporal lesions involving AI: cortical deafness (with no response to pure tones and to speech, but with normal brain stem auditory evoked potentials and absent middle latency auditory evoked potentials), verbal agnosia (normal pure tone threshold, with capacity to recognize complex sounds from the environment, but with absent comprehension of speech, and altered capacity to evaluate rapid sound changes) and non-verbal auditory agnosia (pure tone threshold within normal limits, no aphasia, language comprehension preserved, but no capacity to recognize environmental sounds) (rev. Webster and Garey, 1990). Cortical deafness sometimes evolves to auditory agnosia, with a marked overlap with amusia and environmental sound agnosia (Griffiths, 1999). There is a dissociation between perception of pure tones (patients showing no significant changes in the threshold for pure tones and in the discrimination thresholds for frequency and intensity changes) and disorders of complex sound perception (no recognition of complex sounds, like ringing, speech, environmental sounds, and no understanding of spoken language).

Lesions of the auditory cortex have been reported to cause disruptions in the temporal/ rhythmic assessment of sounds. Robin et al. (1990), studying patients with left

and right temporal lobe stroke, reported that each group showed behavioral difficulties in gap detection. Rhythmic assessment can be preserved after excisions of primary areas, but a bilateral lesion seems to be critical for it. Schuppert et al. (2000) studied unilateral lesions with musical parameters- interval and rhythm, contour and metre. They concluded that patients with left hemisphere lesions showed impairment of discrimination of all musical parameters, while patients with right sided lesions showed only impairment of temporal conditions – interval and rhythm. They suggested a hierarchycal organization, with initial right hemisphere recognition of contour and metre, followed by identification of interval and rhythm in the left hemisphere.

CHAPTER 1.4 Studies of the auditory cortex with long latency evoked potentials

Evoked potentials are the recorded responses from the brain (mostly) to peripheral stimuli, either recorded with a short latency from the beginning of the stimulus (short latency auditory potentials) or later (long latency evoked potentials). They are stimulus locked meaning that they represent the nervous system response to the stimulus as it passes the neural generators, providing a direct view over the physiological processes underlying the nervous system response. Possibly they are the closest approach to brain physiology available, since the haemodynamic response seen in functional brain imaging is still delayed by some seconds. Due to these characteristics, evoked potentials represent a good approach to study the auditory cortex and the brain responses to auditory stimulus.

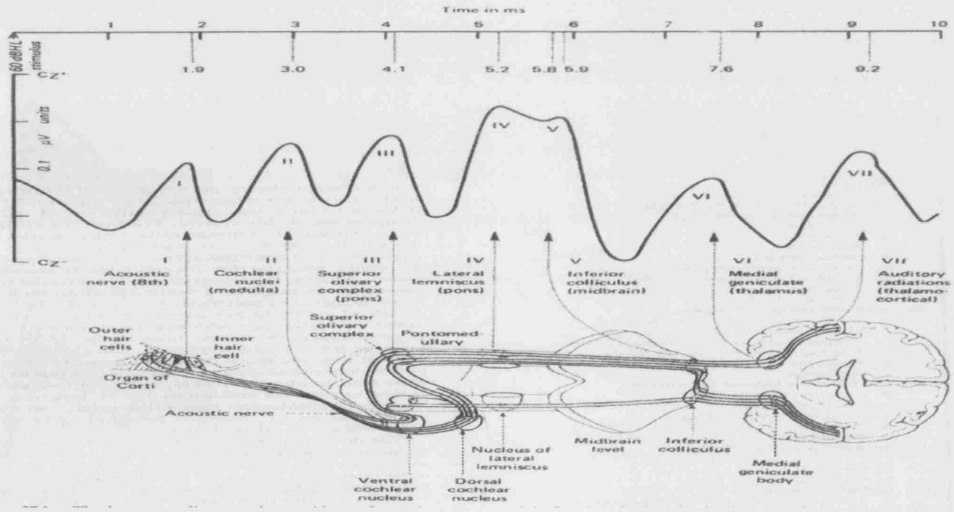

Fig.1-8 Short latency brainstem auditory evoked potentials (BAEP) related with the location of their nuclei of origin (adapted from Webster and Garey, 1990)

Long latency or event related potentials are the late deflections produced by an auditory stimulus, presumably corresponding to the processing of information in various regions of the brain. Classification presents several problems, particularly the fact that the generators are not unitary and so the separation of the components is quite artificial. In spite of this, event related potentials have been classified as "exogenous" and "endogenous" potentials, representing more a continuum than a dichotomous separation. An exogenous component primarily depends upon characteristics of the external stimulus, while an

endogenous component is more dependent upon internal cognitive processes and physiological variables of the subject. There is some oversimplification – actually the exogenous components are shown to be modifiable by attention and the cognitive components are also modifiable by the physical attributes of the stimulus (Coles and Rugg, 1995).

1.4.1 -The N1/P2 component

The auditory N1 is the major negative evoked potential deflection occurring about 100 milliseconds (ms.) after the onset of a sound. It is sometimes preceded by a positive component, the P1 (at 50 ms.), and followed by a positive component, the P2 at 150-200 ms. The N1 peak latency varies about from 70 to 150 ms. after the stimulus and its amplitude is larger at the vertex than at other electrodes and larger contralaterally than ipsilaterally to monoaural stimuli.

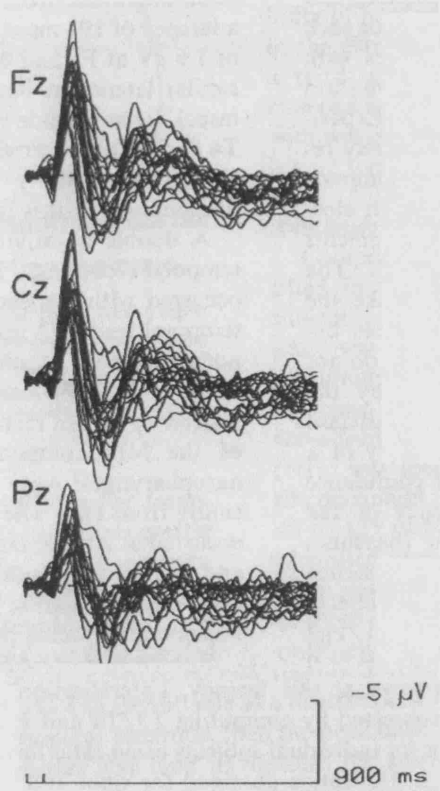

Fig. 1-9. Superimposed individual N1 waveforms from 20 subjects for an auditory stimuli of 90 dB peak SPL, 1.1 seconds (s.) of interstimulus interval (ISI), right ear with a non cephalic reference (adapted by Perrault and Picton, 1984)

N1 is evoked by a relatively abrupt change in the level of energy of the auditory stimulus that induces neuronal responses sufficiently synchronous with each other to generate a field potential (rev. Näätänen and Picton, 1987). Several generators were considered for the N1 wave: Velasco et al. (1985) and Velasco and Velasco (1986) using intracortical implanted electrodes in patients with epilepsy, parkinsonism or with intractable pain found one N1 generator to be located between the mesencephalic nucleus and the ventro lateralis nucleus of the thalamus. A P2 generator was found between the ventro lateralis nucleus and the dorsal thalamus and between the fronto limbic and striatal regions. Most other evidence, however, suggests N1 to be generated in the cerebral cortex (see Näätänen and Picton 1987, for a review). Godey et al. (2001) compared intracerebral responses obtained over the auditory cortex with magnetoencephalographic responses. While N1 was generated in the intermediate and lateral parts of the Heschl's gyrus and the planum temporale, P2 had several possible locations, changing location in different patients to the same task, implying a more complex generator.

The N1/P2 waveform is thus not a single response, but comprises specific and non-specific components with multiple generators and overlapping fields. Näätänen and Picton (1987) defined the "true" components of the N1 complex: component I is generated in the cortex of the supratemporal plane (Heschl's gyrus or adjacent regions), with a fronto central scalp distribution. Component II was described by Wolpaw and Penry in 1975 and called the T-complex. It presents a positive peak at 100 ms (Ta) and a negative wave at 150 ms (Tb) which overlaps N1/P2. It is probably generated in the secondary auditory cortex on the lateral aspect of the temporal lobe, activated by connections from AI and the thalamus (eg: Wolpaw and Penry, 1975 and also Scherg and von Crammon, 1986). Component III generators are frontal motor and premotor areas with influence from the ventro lateral nucleus of the thalamus. Component III appears with a large stimulus intensity (> 60dB), has a refractory period of 30s. and shows intermodal refractory effects. Other components of the N1, the mismatch negativity (MMN) and the processing negativity, will occur in response to specific stimulus combinations or attention inducing stimulus. MMN will be described later in more detail.

The N1 response relates more to the absolute physical characteristics of the stimulus to be analyzed than to the degree of deviance from the preceding stimulus. In fact, when comparing two stimuli with the same intensity deviance from the previous sound, one higher and one lower, the lower intensity stimulus produces a smaller N1. The N1/P2

potential thus seems to be more related to the appreciation of the tone characteristics than to the assessement of the degree of deviance from the previous tone, and so to the allocation of it to a similar or different sound source.

When produced by brief pure tones, the amplitude of N1 depends to various degrees on the physical similarity of the repetitive stimuli, the intensity and the frequency of stimulus occurrance. In a similar way, N1/P2 latency is also dependent on stimulus intensity, with latency being longer at low level presentations of the stimulus, while prolonged latency is also observed for low frequency stimuli (eg: Verkindt et al., 1995). The N1/P2 component is also characterized by a prolonged refractory period, whose duration depends on the N1 component to be affected (I, II or III), and the frequency and intensity of the stimulus used (see Näätänen and Picton, 1987). It presents a short-term attenuation, (which occurs after 3 stimuli at a rate of 0.5 or 1/s. with amplitude decreases of 50 to 75%) and that is a function of the acoustic resemblance of successive stimuli (similarity of frequency).

Näätänen defined the distinction between the two types of change producing an N1: a first type or change-1 responses where the change is from the immediately preceding stable level, generally silence. A second type or change-2 is a form *of change of change* and occurs after successive different presentations of change-1 requiring some neuronal memory of the previous change. A change-1 is seen with the occurrence of sound out of silence, for instance, or when a tone changes frequency. One example of change-2 is the oddball paradigm, in which a standard tone is repeated during a certain amount of time, and is suddenly replaced by a deviant tone (rev. by Näätänen and Picton, 1987). The use of continuous complex tones could produce a change-1 (N1) response even in the absence of silence between the tones. For instance, a N1 response with a similar location in the supratemporal auditory cortex was obtained with continuous tones with changes in frequency (Clynes in 1969) or intensity (Spoor in 1969) (rev. by Näätänen and Picton, 1987). A similar process is seen with the onset responses obtained with magnetic studies (Arlinger et al., 1982; Makëla et al., 1987).

Probably due to the multiple generators involved, lesional studies of the N1 provided inconclusive findings. Peronnet reported that the inversion of polarity of the N1 across the Sylvian fissure disappeared ipsilaterally with lesions affecting the temporal cortex (Peronnet et al., 1974). Knight found a much smaller N1 with temporo-parietal lesions, showing no vertex predominance, while P2 did not show any change in amplitude

or latency. Frontal lobe lesions did not produce any difference in ipsilateral scalp recordings, but they remarkably caused an increase in N1 amplitude in the contralateral side (Knight et al., 1980). Woods reported that unilateral temporal lobe lesions would affect the P1 component in both hemispheres, with a bilateral decrease of one of the N1 generators while P2 would only be affected by anterior temporal lesions (Woods et al., 1987). Verleger et al. (1994) also found that temporo- parietal lesions would decrease both the N1 and the P3b components in amplitude. On the other hand lesions in both temporal lobes might completely abolish the N1 or leave it entirely normal, depending on the extension of the lesions. Woods et al., (1984) reported a normal N1 from a cortically deaf patient. The authors suggested that, since cortically deaf patients due to bilateral auditory cortex lesions can present N1/P2 responses to sound, the N1/P2 could reflect the functioning of a system which is necessary but not sufficient for auditory discrimination.

Although difficult to study, due to its complexity, the observed changes in the N1 auditory response with different types of lesions suggested that a surgical lesion in the temporal pole could also affect auditory responses that are suspected to be generated at or near the temporal pole.

1.4.2 -The Mismatch Negativity (MMN)

Näätänen (eg: et al. 1978, for a recent review Picton et al., 2000) using an oddball paradigm with deviants in intensity and frequency obtained a potential called "mismatch negativity" (MMN), relating its presence to a mismatch between a memory trace formed by the regular stimulus (the standard) and the appearance of a new stimulus (the deviant).

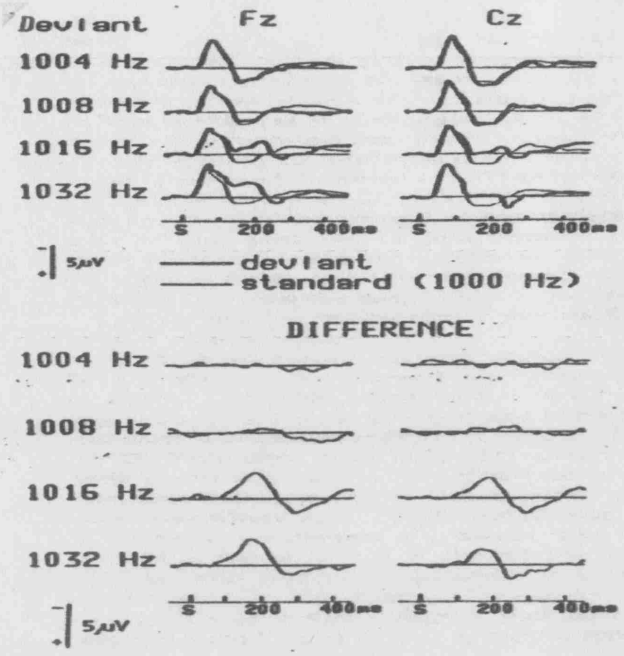

Fig.1-10 MMN to small changes in frequency to a standard stimulus of 1000Hz (adapted from Näätänen and Picton, 1987). The above figure shows the sum of standard and deviant responses, while below the figure obtained with the difference between standard and deviant responses represents the MMN responses.

The MMN should probably be considered an exogenous component of the auditory evoked potentials because it can be elicited in subjects who are not required to attend or respond to the stimulus. While the standard stimulus evokes an N1-P2 response, the deviant response contains two negative waves, a negativity with similar latency as the N1 and a later negativity, the MMN. Subtracting the standard response from the response to the deviant isolates this last component.

A different scalp distribution is observed between N1 and MMN, with the latter showing a more frontal distribution. This difference is confirmed by magnetoencephalographic studies showing a separation between the N1m and the MMNm (the magnetic equivalent of both components (see Alho, 1995 and Picton et al., 2000 for a review). Different scalp topography of the MMN dipoles was reported according to the type of stimulus change (intensity, frequency or duration) suggesting different neuronal populations involved in sensory memory representations for the different characteristics of sound (rev. Alho, 1995).

Very early MMN sub components may be generated in the thalamus as indicated by intracranial recordings in the cat and in the guinea pig. This suggests that comparisons between current and preceding auditory input may occur before its arrival in the cortex-

with a possible role of the hippocampus (rev. Alho, 1995). However, intracranial recordings in humans did not record any MMN from the hippocampus, amygdala, basal ganglia or thalamus (Kropotov et al., 1995). Intracerebral electrode studies in humans disclosed a MMN response that started at 130 ms and peaked at 230 ms in Brodman area 21, and that started at 80 ms and peaked at 130ms in Brodman area 42. In area 42, the MMN was followed by a positivity- possibly the P3a component- even in the passive /listening conditions (Kropotov et al., 1995). Giard et al. (1990) reported that magnetoencephalographic and dipole analysis suggested that MMN generators are located bilaterally in the auditory cortex, with an additional contribution from the right frontal cortex. This frontal activity was believed to be concerned with the process of triggering attention passively, in order to switch it to deviant events (eg: Näätänen et al., 1992) or to target events. The MMN could, then, result from the activity of neurons sensitive to the changed stimulus features, which are less refractory than the neurons responding to the standard pulse (Schröger et al., 1997). Backward masking (obtained when a tone is followed closely by a stronger tone, the response to the first tone being affected) affects the MMN response, suggesting an involvement of neurons containing auditory sensory memory (Winkler et al., 1993, Winkler and Czigler, 1998). The functional role of the MMN has been suggested to be either an automatic system for discriminating sequential sounds, or as a mean of representing auditory constancy. Both explanations are not entirely exclusive and it is likely that they are complementary interpretations of a similar mechanism - in order to evaluate a change in the input, a representation of constancy must be held.

The MMN amplitude to frequency deviation in pure tones typically varies between 0.5 and 2 microvolts, and its latency varies between 100 and 200 ms., both dependent on the magnitude of stimulus deviance from the standard. There is convincing evidence for the relationship between behavioural discrimination threshold and MMN amplitude (rev. Lang et al., 1995). However the amplitude of the MMN seems to attain a saturation point for frequency deviants, not increasing with increased deviance while the MMN to intensity deviants continues increasing (Näätänen et al., 1989). The MMN can be obtained in response to interstimulus interval (ISI) between standard and deviants varying between 0 ms. to 12 s. (rev. Winkler et al., 2001). A dependence on ISI is noted: as the ISI gets longer, MMN latency becomes longer as well and its amplitude becomes lower, suggesting an

increasing difficulty for deviant recognition (Schröger and Winkler, 1995) although an effect of attention can also be claimed for long duration stimuli.

Pure tones were used initially to evoke the MMN, possibly in order to simplify the responses and the consequent explanations. The deviants for MMN with pure tones were changes in frequency (Sams et al., 1985), in intensity (Näätänen et al., 1987), or in spatial location (Paavilainen et al., 1989). The MMN was also obtained with different kinds of temporal or rhythmic changes in sequences of pure tones, such as a stimulus repetition in a sequence of two alternating tones (Nordby et al., 1988; Tervaniemi et al., 1994) or changes in stimulus duration (Kaurokanta et al., 1989), ISI duration (Nordby et al., 1988) or changes in a rhythmic stimulus pattern formed by several tones (Imada et al., 1993). The presence of MMN to changes in ISI suggested that the temporal parameters of acoustic stimulation are also encoded in memory traces which become representations of the auditory events rather than static stimulus aspects. The presence of the MMN to pairs of tones descending in frequency, following standard pairs of ascending frequencies, (although the actual frequencies were allowed to vary), indicates the capacity of the MMN system to identify more complex stimuli than a simple change from the preceding sound (Saarinen et al., 1992). The evaluation of multiple deviants either alone or summated allowed the definition of different generators loci for each deviant (Wolf and Schröger, 2001; Paavilainen et al., 2001) and with a possible parallel processing.

The MMN latency is shorter and its amplitude is larger for complex than for simple tones. Patterns of complex tones were used as standards for elicitation of the MMN or of its magnetic counterpart, the MMNm. This was either for the infrequent exchange or duplication of segments in a complex tonal pattern (Schröger, 1992, et al., 1994), or for duration differences (Alain et al., 1999) or changes in intensity (Schröger et al., 1996), confirming that the temporal structure of the sound is encoded and that there is an automatic detection of periodicity in the acoustic stream. All these changes supported the notion that the MMN is dependent on the pattern of temporal and spectral information (Schröger et al., 1994), and that spectral and temporal elements of the sound are encoded together (Alain et al., 1999).

Lesional studies suggested that unilateral lesions at the temporo-parietal junction did not affect the MMN (Woods et al., 1993). Aaltonen (et al., 1993) compared MMN responses to tones and vowels in patients with left hemisphere damage, and found that patients with posterior temporal lesions failed to show a MMN response to vowels. Patients

with left hemisphere stroke showed a reduced MMN to deviants in duration (Ilvonen et al., 2001) while patients with right hemisphere damage and neglect presented a reduced response to deviants in spatial location, but no changes to duration deviants (Deouell et al., 2000). Lesions in the dorsolateral prefrontal cortex reduce the MMN to frequency deviants, especially on the right and to the ipsilateral ear (Alho et al., 1994). Effects of subcortical lesions can also be seen: unilateral lesions of the anteromedial nuclei of thalamus, sparing the auditory thalamic nuclei, caused an attenuation or absence of the MMNm to binaural tones with a normal N1m, suggesting a subcortical influence on the pre-attentive processing of sound (Makëla et al., 1998).

The equivalent current dipole of the MMNm is located in the supratemporal auditory cortex, in or in the vicinity of the primary auditory cortex, anterior to the supratemporal generators of the N1m (eg: Hari et al., 1984; Sams et al., 1985). It is possible that two different or partially different populations of neurons are involved in processing changes in simple and complex tones, since the MMNm to a deviant complex tone is obtained 10 mm medially to the source of the MMNm for the same degree of frequency deviation in a simple tone. Responses to a musical chord or musical tones peaked earlier and were larger over the right hemisphere compared with responses to a pure tone changing similarly (Alho et al., 1996; Levänen et al., 1996). When the P3a is present sequentially after the MMNm, its generators are also apparently located in the superior temporal plane, but intracranial recordings suggest its origin in the limbic structures, namely the hippocampus (Kropotov et al., 2000). The suggestion of differential activation of both hemispheres by the same stimuli comes from a study by Levänen, that described one MMNm source on the left hemisphere, activated later than the two sources on the right hemisphere (right temporal lobe and right inferior parietal lobe) by a sound sequence with deviants in duration, frequency and ISI (Levänen et al., 1996).

The classic odd ball presentation with random occurrence of the deviants is not necessary for the presence of MMN: there are no significant differences with random or regular presentations of the deviant as long as the deviant is still distinguishable. Due to these characteristics it was concluded that the MMN needs a recent memory of the standard, but also a record of invariances and interactions for a longer period, in order to extract more complex regularities from the sound pattern. These long and short memory stores constitute the auditory sensory memory.

The auditory sensory memory refers to the ability of the auditory system to retain transient representations of the physical features of auditory stimuli for short periods. It is a pre categorical type of memory divided into two types of stores: the short auditory store with a limit of around 300 ms., whose function is to replace sound representation in echoic memory, and the long auditory store (echoic memory) with a limit of around 10 s. (rev. Cowan, 1984). It is possible that the echoic memory functions as an ongoing source of acoustic information to categorical or working memory during and beyond the process of stimulus identification. In this memory trace formation process, both parallel and sequential temporal integration of sensory information occurs.

The MMN provides the best available physiological measure of automatic central processing in audition and is thus potentially a useful tool in the study of auditory pathology (rev. Kraus et al., 1995). The presence of the MMN in comatose patients seems to be related with a better prognosis (Kane et al., 1996; Fischer et al., 1999). MMN abnormalities in mental diseases such as schizophrenia and in neurodegenerative conditions such as Parkinson's and Alzheimer's disease suggest the involvement of pre attentive auditory processes in these pathologies (rev. Pekkonen, 2000). However, a great inter-individual variability accompanied by a low signal to noise ratio makes the potential not useful for widespread clinical use. Essentially, the clinical abnormalities described are for patients' groups and not for individual patients. The low amplitude and the low signal to noise ratio would prevent the use of the MMN to evaluate individual responses in patients undergoing epilepsy surgery and its possible relation with the neuropsychological changes observed.

CHAPTER 1.5 Auditory responses to spectral and temporal changes in a continuous tone

In order to analyze the continuous and complex sounds of the environment, the auditory system starts by deconstructing the sound into its constituent frequencies at the cochlear level. How this information is again regrouped and becomes coherent, forming sound objects, is still a mystery that single unit and pure tone studies have not yet solved. If we wish to understand how the auditory system reconstructs sound objects from their peripheral spectral components, and how a pathological situation can change this sytem, more complex stimuli are needed, "in order to evoke auditory activity resulting from a concerted action of neural networks" (Shamma, 2000). Since an auditory stimulus is defined in terms of spatial, temporal and spectral components, the higher functions associated with what is called auditory scene analysis (Bregman, 1990) would include the simultaneous evaluation of the spatial origin, the spectral envelope and the spectro-temporal pattern of the sound, in order to allocate sounds of similar origin to the same sound stream (grouping). These higher auditory functions also include following an auditory object in respect of its changes over time and how the auditory object can be resolved from the auditory background.

In electrophysiology, complex tones started to be used discontinuously as in the oddball paradigm, or continuously, with the later studies suggesting the existence of a different way of detecting the MMN. The following is a summary of previous findings on auditory evoked potentials obtained with continuous complex tones, producing responses that are believed to be related to high order sound analysis.

The long latency evoked response to sound onset after silence (N1, or onset N1 in order to distinguish it from the accompanying potentials) is a complex response, with the change from silence to sound involving systems to localize the incoming sound in space, to analyze its spectrum and its temporal pattern, all working together. The Onset N1 (ON1) and associated potentials may then be related to a change in spectrum, in timing and in localization of the sound.

1.5.1 -The spectral analysis- the "C process"

A progressive transition between discontinuous and continuous complex tones (using synthesized musical instrumental sounds) that changed in pitch every few seconds produced, when the gaps between tones were less than 200 ms, an evoked response consisting of a small P1 at 60 ms., a N1 larger at Cz than Fz and a very large P2 (Jones et al., 1998).

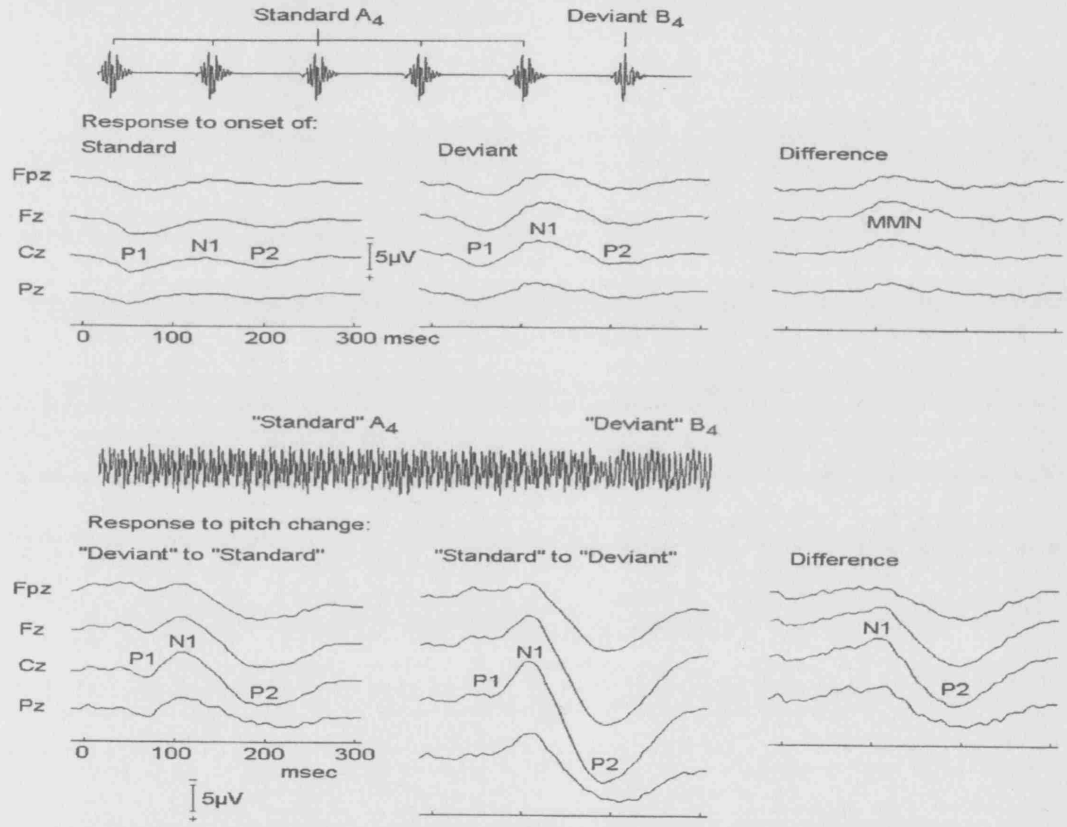

Fig. 1-11 Comparison of the odd-ball paradigm and the change in pitch in continuous complex tones. Above, the representation of the MMN, below, the representation of the CN1 (adapted from Vaz Pato and Jones, 1999).

Similar P1/N1/P2 responses were obtained with small and large pitch changes ranging from a semitone (6% in frequency terms) to an octave (100% in frequency terms) and also when tones of constant pitch alternated between instruments of different timbre. The introduction of a silent gap of more than 200 ms. between the tones changed the N1/P2 morphology, with the N1 becoming more frontally distributed, and the P2 becoming

smaller than the P2 recorded with continuous tones, as seen for ON1. In the same experience, when the same tones changed pitch at increasing rates (1, 2, 4, 8 and 16 Hz), these particulars N1-P2 responses were progressively attenuated, but an interspersed timbre change every 2s. produced again a large P1/N1/P2 response as the one obtained with slow rates of pitch change. A constant interfering background tone of similar timbre caused a greater attenuation of the P1/N1/P2 response to pitch change, as compared with the effect of an interfering tone of different timbre to the changing one (Jones et al., 1998). This response to continuous tones changing in spectral content (pitch or timbre) was called Change-type N1 and P2- CN1, CP2.

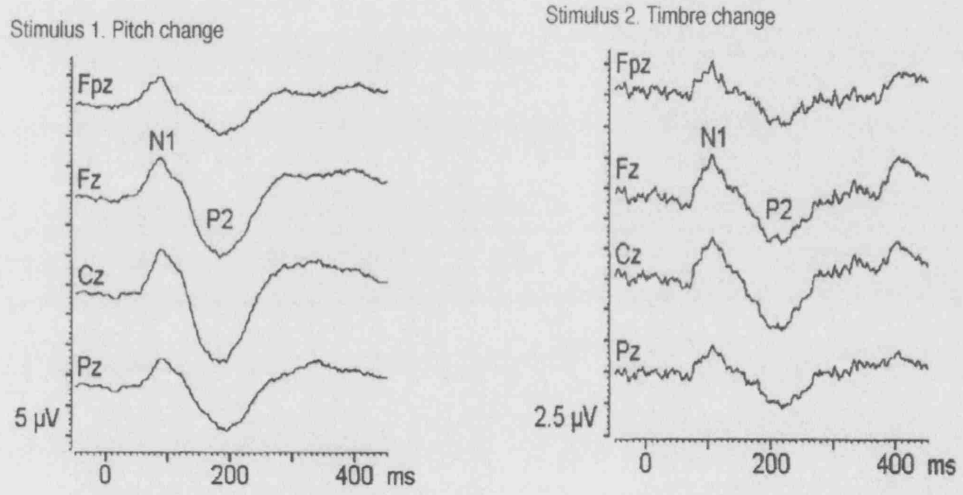

Fig. 1-12 CN1 to pitch and timbre change in continuous complex tones (adapted from Jones et al., 1999)

The CN1 amplitude was up to 10 µV in amplitude and the CN1-CP2 peaks occurred at c.100 and 180 ms. respectively, after the spectral changes which elicited them. The fact that both changes in pitch (defined by the spectral elements moving in geometric proportion along the frequency axis) and changes in timbre (defined by most of the components changing only their energy values- spectral envelope) produced similar responses suggested the existence of a non-specific process of spectral change analysis.

In a later study using synthesized "Clarinet" tones, auditory evoked potentials were recorded to alternating pitch changes of 1 or 7 semitones occurring every 0.5s. or every 1.5s. and to a cycle of 6 pitches changing every 0.5s. Little or no difference was found in

the amplitude of the CN1/CP2 in relation to the magnitude of the pitch change. The amplitude was not strongly influenced by the interval between occurrences of the same pitch, but was strongly related to the rate at which changes occurred. In the same experiment, pitch changes of high and low pass filtered tones (the former consisting only of the fundamental, the later consisting of the high partials of the tone) suggested an influence of the width of the changing frequency spectrum on the auditory evoked potentials amplitude, with upper partials contributing more than the fundamental frequency (Jones and Perez, 2001). Hence, the amplitude of the CN1 is strongly dependent on the rate of occurrences of pitch change in the cycle, and the width of the changing spectrum, but not on the refractoriness of a particular population of frequency specific neurons.

It was suggested that the 200 ms. gap limit which appears to be critical for the full expression of the C-potential might correspond to the duration of the short auditory store and that the presence of both tones within this time frame might start a process of spectral change analysis, involving some neurons located more posteriorly on the supratemporal plane than those responding to the onset of tone (Jones et al., 1998). However, the morphology and distribution of the CN1/CP2 points to a similar generator as the ON1/OP2 response. The amplitude of the CN1 potential is also influenced by the duration of a preceding steady pitch up at least to 4.5s. (Jones et al., 2000 a). This is similar to some estimates of the duration of the long auditory store, so the evidence suggests that both stores may be involved in the generation of the CN1. The spectral analysis that seems to underlie these components suggests that the C- process is a possible candidate for reflecting the action of neuronal networks located higher in a multiscale representation system, and which may be more specialized in detecting spectral changes than the ones signalling onset of sound (Shamma, 2000).

1.5.2 -The spectro-temporal analysis- the M process.

When pitch changes in a continuous tone are made at a progressively increasing rate, the associated C-potential becomes progressively attenuated. At a rate of 8 or 12 changes/s., small oscillatory potentials were still present, but they were virtually abolished at 16 changes/s. When these changes abruptly ceased, they revealed a negativity followed by a positivity occurring with the steady tone (Vaz Pato and Jones, 1999). The variation of

modulation rate revealed that the negativity/positivity latency is related not to the onset of the steady tone, but to the next expected change that did not occur.

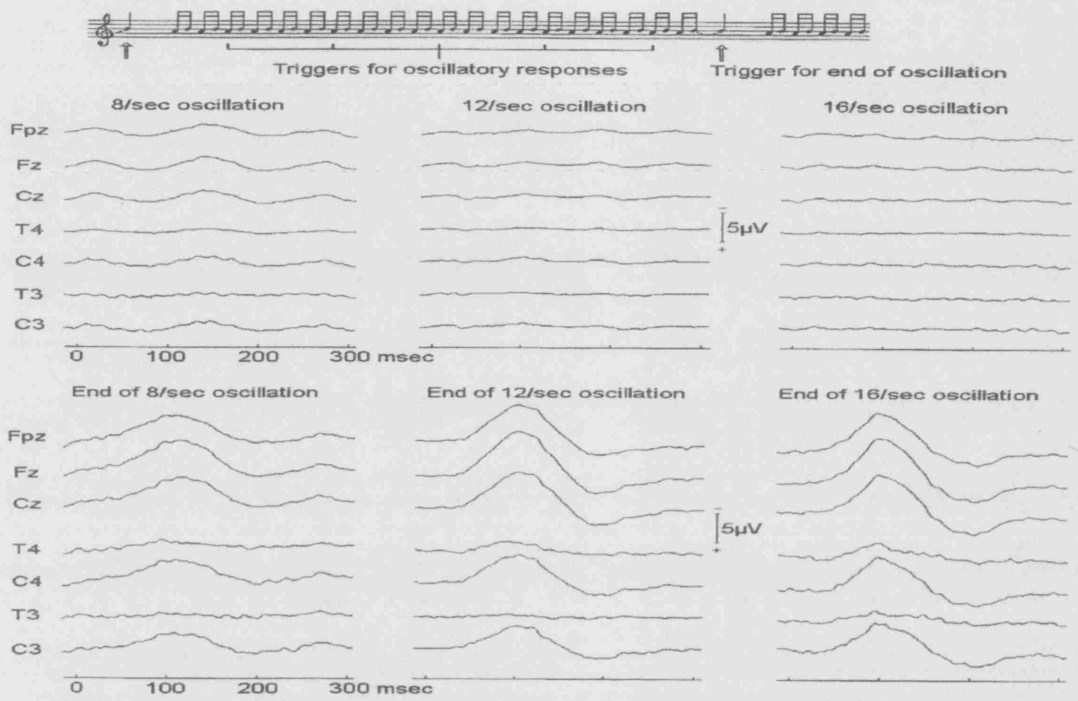

Fig.1-13 Evoked responses to end of oscillation with 8, 12 and 16Hz (adapted from Vaz Pato and Jones, 1999).

It seems that the immediate incoming sound is compared with a template of the preceding modulation pattern, which is extrapolated so as to predict the time when the next change should occur. The negativity/ positivity response that takes place when the next expected change does not occur was called "Mismatch-type" N1-P2 - MN1 and MP2. The MN1 response to a steady tone, after a period of rapid pitch changes, peaks around 100-120 ms., and is more anteriorly distributed than the ON1 or the CN1 described previously. It is also produced by a deviant tone in a continuous pattern (Vaz Pato et al., 2002). It is maximal at Fz, symmetrically distributed and with amplitude up to about 7μV.

The MN1 amplitude was found to be influenced by the regularity of the preceding pattern: in an experiment varying the characteristics of the standard period of oscillations, comparing rhythmic with non-rhythmic patterns of tones (both composed of the same pitches), the MN1 response to the same deviant was significantly larger when the standard tones were in a rhythmic pattern. The latency of the MN1 response was not affected by the regularity of the pattern, but by the degree of pitch deviance. In the same experiment,

sequential pitch deviants in a repeating pattern of 5 pitches presented at 16 tones/s. evoked two sequential responses, while a third deviant produced a less consistent response. This would implicate the M response as part of a process of temporal pattern analysis, more than a simple change detector and/or an attention orienting mechanism (Vaz Pato et al., 2002).

An experiment in which the duration of the oscillating period (16Hz) and of the steady tone varied reciprocally within a duty cycle of five seconds showed a monotonic increase of CN1 and MN1 amplitudes related with the duration of the preceding stimuli (steady for the CN1, oscillating for the MN1) (Jones et al., 2000 a). Both CN1 and MN1 amplitudes were 3-4 times larger after 4.5s. as compared with 0.5s. duration of the previous sound pattern. This cannot be explained by simple refractoriness, since the responses occurred once every 5s., regardless of the partition of that period into steady or oscillating pitch. Rather, the findings suggest the participation of a sensory memory store of at least 4.5s. duration, with responses of maximal amplitude being generated when the store is "full" of a particular pattern.

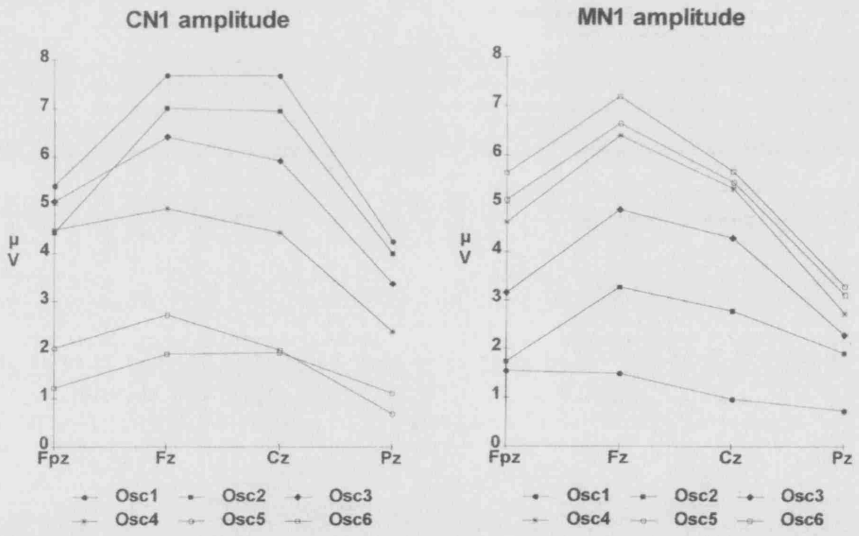

Fig. 5. Sagittal profile of mean CN1 and MN1 amplitudes at 4 midline scalp electrodes in each condition.

Fig.1-14. Changes in CN1 and MN1 amplitudes along the different conditions, with a progressive increase in amplitude related with the duration of the previous stimuli (adapted from Jones et al., 2000).

It is arguable that when CN1 is made refractory by a high rate of changes between two frequencies, the response recorded when a new frequency occurs, might be due to a new, frequency specific population. However CN1 responses do not occur with tones of longer duration as is the case when the oscillatory pattern stops on a steady pitch (a duration deviant). Furthermore, this would not explain the more anterior distribution of the

MN1 as compared with the CN1. The occurrence of a steady pitch after a tone oscillation period between this pitch and another has similarities with a duration deviant, in which similar frequencies are present but for a longer period of time.

Picton et al. (2000) argues that a duration deviant is the least contaminated form of MMN, since the N1 response is not present, as no new frequencies are present in the sound. Possibly, the MN1 is a pure form of the MMN, without the contamination of the CN1. Although the correspondence between MN1 and MMN potentials may not be complete, the MN1, like the MMN, is usually maximal at Fz. Both potentials have a shorter latency with greater degrees of deviance from the standard, and both can be explained by the same underlying mismatch process between the incoming sound and a template of the preceding sequence of sounds

The MN1 is larger than the usual MMN, possibly due to the summation of the numerous frequencies of complex tones when compared with the pure tones usually used to evoke the MMN. The MMN has also been reported to be larger with complex tones (Tervaniemi et al., 1993). Also, it is possible that since there is no silent gap between the tones, there is no opportunity for the decaying of the standard sound image in the long auditory store, producing a larger response to the deviant sound.

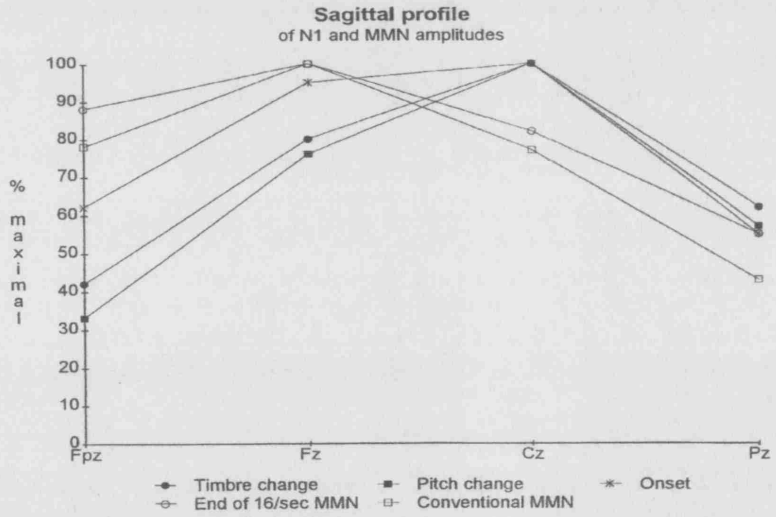

Fig. 1-15 Comparison of CN1, MN1 and MMN amplitude scalp distribution (adapted from Vaz Pato and Jones, 1999)

The CN1 and the MN1 are apparently generated by functionally different populations of neurons in the supratemporal plane, with the MN1 generators being the more anterior, possibly located in secondary areas of the auditory cortex (Jones et al. 1998, Jones

et al., 2000a) while the CN1 is generated in the primary region. Some clinical applications have been explored using these potentials: a preliminary study with four unsedated comatose patients showed no consistent responses for two patients, while CN1 was present and MN1 absent in one patient, both components being present in one patient who was beginning to show signs of responsiveness. In a group of post comatose patients, the presence/ absence of the auditory responses (CN1 and MN1) was significantly correlated with the behavioural ability to respond to verbal commands, suggesting a new tool to evaluate the capacity for discriminative hearing in these patients, not dependent on their ability to signal this perception (Jones et al., 2000 b). In this study, seventy- five per cent of MN1 responses were abnormally delayed, particularly in the cases with traumatic brain injury. A third clinical study was performed in a group of patients with definite multiple sclerosis in whom Onset and C-potentials, although abnormal in some individual patients, did not show any significant group effect. However, the MP2 responses, and less notably MN1, were delayed when compared with normal controls. These results may be related to the deterioration of higher cortical processes in MS patients, specifically the processing of change in temporal sound patterns (Jones et al., 2002).

1.5.3 -The positive components and the T-complex

A P1 component is consistently recorded, preceding the CN1 by about 40 ms. to spectral energy changes in continuous complex tones. When the MN1 to the end of an oscillating cycle is obtained, no preceding P1 is seen, although when the MN1 is produced by a frequency deviant tone in a sequence of tones, there is usually a preceding P1. Middle latency auditory responses are characterized by several scalp or vertex positive and negative peaks, of which the P1 (Pb or P50) is a prominent one. Its generators are believed to be thalamic nuclei receiving a strong contribution from the mid-brain activating system, although magnetic and electric studies points also to a cortical temporal lobe source (rev. Kraus and McGee, 1994).

The small and frontal OP2 becomes larger and more central when the changing spectral frequencies are presented with a "gap" of less than 200 ms.- and becomes CP2, already described. The end of an oscillating sequence of a tone changing in pitch, when resting on a steady pitch, elicits a MP2 potential following the MN1, with the same frontal distribution (Vaz Pato and Jones, 1999, Jones et al., 2000). A positivity is also present after the classic MMN and is thought to be the P3a, a positivity occurring in response to large

stimulus differences whether or not the subject is actively paying attention to the stimulus sequence. The P3a is believed to be generated in the supratemporal cortex but other authors suggest its origin in the limbic structures including the hippocampus (rev. Kraus et al., 1994).

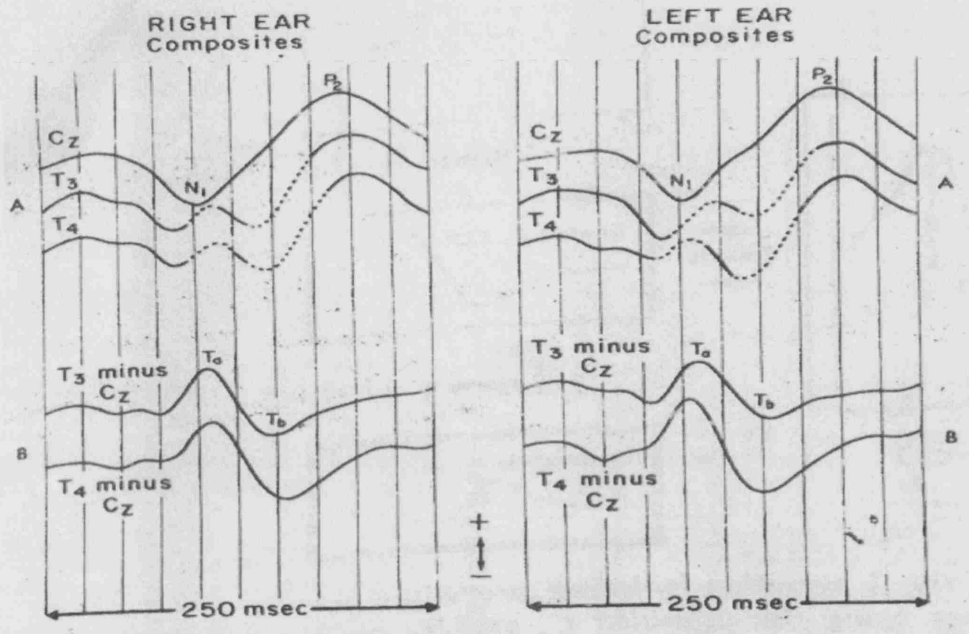

Fig. 1-16. A T complex is seen at temporal electrodes consisting of a negativity (Ta) peaking around 140ms. and a positivity (Tb) peaking about 200ms (Wolpaw and Penry 1975)

A "T-complex", was recorded at the temporal electrodes (T3 and T4). It was already described with right side predominance following click stimuli (Wolpaw and Penry, 1975). Brief tone bursts failed to confirm this asymmetry (Connolly,1993; Scherg and von Cramon, 1986) and a symmetrically distributed T complex was also seen with changes in the interaural time difference of dichotically presented noise (Jones, 1991). However, with musical chords, the T-complex was larger at right temporal electrodes (Taub et al., 1976) suggesting that the lateralisation of the T- complex is dependent on the type of stimuli used. Using continuous complex tones, the T complex is consistently recorded in association with Onset and Change N1 and P2, although not always in association with the M-response. The recording of auditory evoked potentials to onset and offset of synthethised instrumental tones in right- and left-handed subjects showed a converse laterality of the T-complex in left-handers in a proportion in accordance with the expected proportion of left-handers to

have right hemisphere dominance for language. This suggests that AEPs to complex tones may prove a useful tool in establishing functional lateralization (Jones and Byrne, 1998).

CHAPTER 1.6 Temporal lobe epilepsy

Epilepsy is a neurological disorder, producing a paroxysmal electric activity of the brain that results in epileptic seizures. These seizures can be partial, affecting only one neurological system (motor, sensitive, high functions), or generalized, and all the systems are affected, resulting sometimes in loss of consciousness and major damage to the patient. Most patients can be treated with anti-epileptic drugs, but some forms of the disease are particularly resistent to medical treatment.

Temporal lobe epilepsy is a general designation for different seizure types of temporal lobe origin. Several classifications exist, one helpful distinction being between mesiobasal and lateral neocortical types (rev. Duncan, 2000). Mesiobasal or mesial temporal lobe epilepsy, sometimes known as limbic epilepsy, is mostly associated with hippocampal sclerosis (although other etiological factors such as benign tumours, arteriovenous malformations or neurological migrational defects can also be involved) and represents a clinically recognizable syndrome associated with specific clinical, electroencephalographic, neuropsychological and imaging features (Engel et al., 1997).

The aetiology of temporal lobe epilepsy is not completely clarified. The term medial temporal sclerosis was used to imply gliosis and loss of neurons within the hippocampus, subicullum, parahippocampal gyrus, and amygdala and inferomedial temporal cortex and is now recognized as the most common pathological finding in adults with temporal lobe epilepsy. It is present in 50-75% of temporal lobe resections performed for intractable limbic epilepsy. Since the hippocampus is very sensitive to pathological stimuli, factors like febrile seizures, meningitis, trauma and infection frequently led to the appearance of mesial temporal sclerosis, particularly in children. Patients with temporal lobe epilepsy often have a family history of epilepsy (eg: Falconer, 1971) suggesting an underlying genetic factor. A review of epileptic patients with hippocampal sclerosis showed that 41% had had prolonged seizures or status epilepticus in infancy, 16% had had cerebral trauma, 12% had had non prolonged febrile seizures, 7% had had birth injuries and 10% had had cerebral hypoxia or encephalitis (Matthern et al., 1994, 1995 a).

Temporal lobe seizures secondary to hippocampal sclerosis are usually responsive to medical treatment for several years, but about 50% of patients characteristically become refractory to medication in adolescence, suggesting some progressive nature of the epileptic

process. This may be related to the sclerotic process in the hippocampus, which seems to progress over time, independently of the time when the initial pathological process is over, even without seizures (Matthern et al., 1995, a).

Clinically, ictal activation of mesial temporal lobe structures produces temporal lobe seizures (also called psychomotor seizures or limbic seizures). The clinical appreciation of the seizures is very important because some of the clinical features occurring with the seizures have localizing features. Some seizures originate only in limbic structures, others in temporal or extra temporal lobe structures but with rapid progression to mesiotemporal structures. Seizures can be simple or complex, generally preceded by an aura, whose duration is 5-60 s. The seizure is followed by a period of dysfunction of variable duration, related to the duration and extent of seizure discharge. During this period, patients are confused, disorientated and show disturbances of language, displaying sometimes a seizure related retrograde amnesia.

Medical treatment may be useful at the beginning of symptoms, but monotherapy is not always possible. With the progression of the disease and the progressively decreased response to a single anti-epileptic drug, 50 to 60% of patients need polytheraphy, with increasing dosages. The long-term prognosis for medication in temporal lobe epilepsy is poor. The diagnostic of temporal lobe epilepsy early in the course of the disorder is important since when medication is not useful, the problem may be eliminated by surgery in 70-80% of patients (rev: Engel et al., 1997). Early surgical intervention implies greatest opportunities for complete psychosocial rehabilitation.

Due to the possibility of secondary effects from surgery, either because of local effects or because of the possibility of bilateral pathology, the localization of the focus is very important. Clinical examination of these patients is not very useful with regards to the localization of the focus, since the neurological examination is generally normal in the period between seizures. Instead, localization of foci is based on electroencephalo-graphy (EEG), long term monitoring EEG/Video telemetry, magnetic resonance imaging (MRI) and, if necessary, invasive EEG video telemetry (used in the pre surgical assessment when the hemisphere or the side of the epileptogenic focus remained unclear after a thorough analysis of the clinical and EEG seizure type). Neuropsychological evaluation can help to localize the seizure focus and also to determine if the memory losses after surgery are going to be profound or not. Other techniques such as positron emission tomography (PET), single photon emission computed tomography (SPECT) or functional magnetic resonance

imaging (fMRI) are more and more frequently used to localize the seizure focus, although still with some limitations (Baxendale, 2002).

An important test for pre surgical-diagnosis is the intracarotid amytal procedure (also called Wada test), used to determine the hemisphere dominance of speech and the memory possibilities of each hemisphere. The Wada test is used when the cerebral dominance is uncertain and when there are suggestions of neuropsychological deficits, implicating dysfunction of the contralateral hemisphere. Because amytal injected into the speech dominant hemisphere produces a transient aphasia, it can be used to determine the dominant hemisphere. The use of simple verbal and memory tests before Wada and during the period in which the affected hemisphere is anesthetized can also demonstrate whether the contralateral hemisphere can sustain basic memory function. A subsidiary role is to find confirmatory evidence of a decreased memory function in the temporal lobe proposed for resection, by using neuropsychological tests when the contralateral side is injected.

Surgery of the temporal lobe for epilepsy has several types of approaches, all dependent on the pre surgical findings. The initial technique of Penfield and Baldwin was an anterior temporal lobectomy with removal of the anterior half of the hippocampus, most of the amygdala and the anterior and lateral temporal cortex. This technique is still used, but it is associated with a significant risk of post surgical memory decline (more in left temporal lobe resections), particularly in patients without hippocampal sclerosis, probably due to the removal of normal tissue responsible for the memory performance simultaneously with the injured brain tissue. Since the most frequent origin of temporal lobe seizures is either the hippocampus or the amygdala, a more selective approach was proposed. The selective amygdalohippocampectomy was initially performed only in patients with hippocampal or amygdala onset of seizures, but it has also been offered to patients with seizure onset in the lateral temporal cortex when the hippocampus has a pacemaker role in seizure spread. Generally, after an incision which allows access to the tip of the anterior horn, the amygdala is removed by suction and the hippocampus and the more anterior parts of the parahippocampal gyrus are then resected en bloc (rev. Wieser, 1994). Both anterior temporal lobectomy and amygdalohippocampectomy showed similar success in the post surgical control of seizures, but the post surgical neuropsychological outcome is dependent on pre surgical assessment: a patient with left temporal lobe epilepsy and good verbal memory may perform worse after anterior temporal lobectomy than amygdalohippocampectomy or lesionectomy (Clusmann et al., 2002). The presence of

hippocampal remnants is also important: Baxendale et al. (2000) reported an improved neuropsychological assessment in patients with hippocampal remnants left in situ and a subsequent deterioration during the period in which these remnants were shrinking. In the long run, a tailored surgical approach (as in amygdalohippocampectomy or lesionectomy) seems to be related to an increased rate of improvements and a decreased rate of losses, with an overall positive effect on post surgical neuropsychological responses.

Prognosis after surgery is dependent on the amount of hippocampal resection: total hippocampectomy versus partial hippocampectomy resulted in 65% versus 38% seizure free patients (Holmes et al., 1997). A good surgical prognosis is also related to factors such as absent or mild post ictal slowing in the electroencephalogram in the contralateral mesial temporal region, with absent or infrequent contralateral seizure discharges, with an anterior mediobasal temporal lobe seizure onset and with a short seizure duration. Outcome is positively correlated with the underlying pathology, being better if there is hippocampal sclerosis, a ganglioglioma or a disembryoplastic neuroepithelial tumour (Clusmann et al., 2002), if there is a history of febrile seizures and/or if there are unilateral material specific memory deficits (Holmes et al., 1997). A good outcome is also related with 100% lateralization of intracranial recorded ictal onset to the surgical place, as well as absence of contralateral dysplasia (Holmes et al., 1997).

The outcome is negatively correlated with the number of preoperative years with seizures, with severe memory deficits and age at the time of surgery. The outcome is also less favourable with bilateral atrophy or no hippocampal atrophy (Berkovic et al., 1995). The previous presence of status epilepticus was also correlated negatively with outcome as well as seizure frequency (Clusmann et al., 2002). Post surgical seizure control was significantly worse in patients with minimal neural loss and no temporal mass lesions in the surgical side compared with patients with hippocampal sclerosis or mass lesions (Matthern et al., 1995, b). An incomplete removal of the lesion appears to be another reason for a less favourable outcome as well as the presence of dual pathology (seen in 5 to 30% of patients with refractory seizures). With dual pathology, as both the lesions are likely to be involved in seizure generation, the outcome will improve with the removal of both (Li et al., 1997).

CHAPTER 1.7 Neuropsychological and neurophysiological aspects of temporal lobe epilepsy before and after surgery

The possible relation between the mismatch negativity and echoic memory, with the latter acting as a server for the working memory function, suggested an eventual relation between MMN results and neuropsychological test results. It is known that epileptic patients often present with neuropsychological deficits due to the different types of seizures the patients have, and/or the pathophysiology or the lesions underlying the seizures as well as their frequency (Bergin et al., 2002). Deficits of attention are well documented in epilepsy and impaired verbal and non verbal memory are seen during sub clinical epileptic discharges (eg: Aarts et al., 1984). Deficits in both cognition and memory are also related to seizure activity, number of years with seizure activity and early age of onset (Bergin et al., 2002). Also, virtually all anti-epileptic drugs can affect mental function, and their use is related with deficits of short term memory, of memory concentration tasks, of attention, of problem solving and of visuomotor tasks (rev: Wieser, 1992). The use of anti-epileptic drugs in mono or in polytheraphy has been demonstrated to be associated with cognitive deficits and slowing of mental speed (Aldenkamp, 2001, but see also Dodrill and Willensky, 1992).

Apart from the use of anti-epileptic drugs, patients with temporal lobe epilepsy show neuropsychological features that are focal and specific. The syndrome is defined by an impairment in psychometrically assessed lateralized memory functions, an anterograde amnesia in the affected lobe when performing the Wada test, and a correlation between the degree of pre-operative to post-operative memory loss, this being related to the pathological status of the hippocampus (rev: Chelune and Loken, 1999). A good correlation was established between neuronal density in certain areas of the hippocampus and both verbal and non-verbal memory and also between MRI measures of the hippocampus and tests of learning and recall (Baxendale, 1995).

The neuropsychological examination of patients with hippocampal sclerosis shows deficits related to the site of the lesion. If the lesion is in the dominant (usually left) hippocampus, the patients manifest deficits on anterograde verbal memory, whereas a right hippocampus lesion is most frequently related to deficits in anterograde non-verbal memory. Pre-surgical assessment of temporal lobe epilepsy patients showed that left

hippocampal sclerosis patients performed worse in naming and in reading comprehension, with difficulties in logical memory for immediate recall, delayed recall, and short and long free recall and retention. This group of patients showed impaired semantic relational processes, possibly due to relational encoding/retrieving difficulties and also cognitive impairments in verbal declarative memory performance, mostly of episodic memory. The right hippocampal sclerosis group showed a worse performance in naming, oral fluency, and in non-verbal visual memory, both for immediate and delayed recall (Hermann et al., 1997). Right temporal lobe patients perform poorly in tachistoscopic presentation of overlapping nonsense figures and have defects in delayed recognition of faces (rev. Chelune and Loken, 1999).

However, it is possible that the separation of functions for both hemispheres is less definite. Studying episodic memory in left temporal lobe epilepsy patients with fMRI, Dupont et al. (2002, b) demonstrated abnormalities in the left hemisphere network activation, but also deficits in the right hemisphere activation and in the bilateral parahippocampal activation as compared with the activation seen in the normal control group. Later, Dupont et al. (2002) used a verbal episodic memory task to assess right temporal lobe epilepsy patients. These patients showed a significantly lower score as compared with the normal control group. They also showed an abnormal bilateral pattern of network activation. The authors suggest the existence of a functional bilateral hemispheric involvement in focal temporal lobe epilepsy associated with well-lateralized hippocampal sclerosis.

From the beginning of epilepsy surgery, cases of bilateral removal of the hippocampus and associated structures presented with profound and irreversible deficits of recent memory and no formation of new long term memory, while the previously acquired memories remained more or less intact. Severe and persistent anterograde amnesia might also develop as an immediate consequence of temporal lobectomy or amygdalohippocampectomy when there is unrecognized pre-existing severe sclerosis of the non operated hippocampus (rev. Trenerry, 1995).

Neuropsychological deficits after surgery can be predicted by several different factors. As previously seen, the integrity of right mesial structures is a significant determinant of memory outcome after left temporal lobectomy. The risk for memory loss after unilateral resections, especially of the dominant hemisphere, depends on the age of the patient at the time of the initial event and at the onset of recurrent seizures, with a long

duration of illness related to poorer outcome. Seizure control is associated with no worsening of neuropsychological deficits due to dysfunction on the surgical side, and with a clear improvement of neuropsychological responses in the normal hemisphere (rev. Wieser, 1992). Age at time of surgery (young patients performing better than old patients) and pre-operative memory performance (a better performance related to more loss) are also related with the outcome. The Wada results correlate with verbal memory function, but not with spatial memory function after surgery (rev. Rausch, 2002). Different expressions of deficits are related to presence/absence of hippocampal sclerosis of the resected tissue: there is a specific vulnerability for episodic versus semantic memory loss among temporal lobe epilepsy patients without significant hippocampal sclerosis in the surgically resected left hippocampus. Post surgical deficits are more marked in patients with relatively limited atrophy of the hippocampus on the MRI, limited histopathological neuronal loss and relatively preserved memory in the temporal lobe to be resected on the Wada test. (rev. Hermann et al., 1995 a and b).

The relationship between lateralized hippocampal pathology and adequacy of memory function is more reliable for verbal memory in the left hemisphere than visual memory in the right hemisphere. A decline in verbal learning and memory following left temporal lobectomy has been found much more consistently than a decline in visual memory following right temporal lobectomy. However, many tests using visual material do not detect deficits in right temporal lobectomy patients, which is consistent with reports that the right hemisphere is involved in the processing of unfamiliar and verbally uninterruptible information (rev.Trenerry, 1995). Barr (1997) suggested that visual tests used to analyze right hemisphere dysfunction should assess independently one of the two visual systems (the ventral system corresponding to "what" and the dorsal system, corresponding to "where") in order to obtain significant results.

Chelune and Loken (1999) mentioned the following changes for pre- and post-surgical neuropsychological assessments: for the right mediobasal temporal group of patients, the pre-surgical ability for learning verbal material improved, as did the capacity for learning figures and learning nonsense drawings. The left mediobasal temporal group of patients demonstrated a reduction in learning verbal material and in learning figures, but an improvement in learning nonsense drawings. The improvement effects on the contralateral hemisphere functions were probably related to the improvement in seizures reported in these patients.

Together with these conclusions, a less clear picture also emerged: it was noted that marked recognition memory defects may not be apparent in either right or left post-surgical individual patients, probably reflecting much inter-individual variation in post-operative change as well as in post-operative seizure control and suggesting a multi factorial effect over the surgical neuropsychological outcome (Hermann et al., 1995b).

Anti-epileptic drug effects on long latency evoked potentials and neuropsychological tests were also studied in normal volunteers, after a 2-week administration of carbamazepine, phenytoin, sodium valproate or zonidazide at therapeutic levels. The use of carbamazepine increased the latency of N1 and reduced N1 amplitude while the use of phenytoin increased N1 amplitude and the use of sodium valproate reduced the latency of N1. Simultaneously, both zonidazide and sodium valproate reduced scores in the neuropsychological attention tests (Akaho, 1996). In other studies polytheraphy effects were analyzed: epileptic patients on monotherapy showed shortened long latency evoked potential latencies when compared with patients on polytherapy (Triantafyllou et al., 1992), while the reduction in the number and dosage of anti-epileptic drugs during one week for pre-surgical assessment caused decreased N1 latencies (Tuunainen et al., 1995).

Verleger et al. (1997) compared N1 in patients with secondary partial seizures and patients with idiopathic generalized epilepsy. The N1 component was not significantly different from the control group in the group with partial seizures, but was delayed in the patients with idiopathic generalised epilepsy. This delay was related to a longer period of epilepsy, the number of seizures/month and the number of anti-epileptic drugs used. Other factors may also affect N1 responses: non-controlled patients showed reduced N1 amplitudes in sphenoidal recordings, ipsilateral to the epileptic focus with no contralateral effect, while in controlled patients, the asymmetries of the evoked responses were less apparent (Tuunainen et al., 1995).

In an extensive literature review, there were apparently no articles of MMN on epileptic patients. MMN was evaluated in patients with vascular lesions of the hippocampus, in comparison with other temporal lobe lesions (Alain et al., 1998). The authors did not discover any latency difference for the component in patients with hippocampal lesions, as compared with patients with dorsolateral temporal lesions, the latter presenting MMN delayed latencies when compared with normal controls. MMN was also recorded with intracranial electrodes in pre surgical children in response to complex sounds and tones, peaking at 128 ms., with complex sounds producing a two-fold increase

in amplitude. This MMN response was recorded in Brodman's area 45 (right lateral pre frontal cortex) (Liasis et al., 2001). Potentials reflecting detection of deviance in tones and syllables were also recorded in 4 pre surgical epileptic children by the same authors, with a latency of 68 ms., around the Sylvian fissure (Liasis et al., 1999). MMN to frequency deviants overlapped with N1 responses in one pre-surgical epileptic child, while MMN to duration deviants peaked 100 ms. later (Liasis et al., 2000).

Post-surgical studies were performed in an attempt to quantify event related potential abnormalities due to surgical intervention and to relate findings with the neuropsychological changes obtained in these patients. Studies concerning the N1 potential after epilepsy surgery described no change either in scalp recordings or in magnetoencephalographic recordings (Mervaala et al., 1992). However, other authors described reduced amplitude of the N1 post surgically but at scalp sites not related with the affected temporal lobe (Tuunainen et al., 1995). Nakasato et al. (1997) described a N1 bilaterally attenuated after a unilateral temporal lobe resection while Johnson (1989) studied temporal lobe epilepsy patients ten years after surgery and described a larger N1 on the resected hemisphere, suggesting that this might be due to the resulting skull defect.

There were apparently no published papers discussing MMN potentials in patients submitted to temporal lobe surgery. Several studies with pre- and post-surgical patients were performed using the P300 component. However, the complexity of this potential and the apparent absence of a relationship between the pre-attentive potentials and the P300 make an exhaustive reporting irrelevant.

1.8 Hypothesis:

The anterior location of the MN1/MP2 and its possible relation with the hippocampus raise the question whether this component may be particularly vulnerable to a surgical procedure affecting the anterior temporal pole. The first hypothesis of the present study is that, due to the possible relationship between MN1/MP2 and the hippocampus, the MN1/MP2 response may be different in a population of patients with hippocampal sclerosis, and that the difference may be lateralised to the affected hemisphere prior to the surgical procedure.

The second hypothesis of this work is that the MN1/MP2 component may be affected in amplitude and/or in latency after epilepsy surgery, due to the removal of the hippocampus and/or the anterior temporal pole. Due to its presumed more posterior location, the CN1/CP2 generators might not suffer any direct effect, while the ON1/OP2 component (probably with multiple generators) might show a lesser effect.

The third hypothesis is that, due to the possible relation between CN1/CP2 and MN1/MP2 and the echoic memory (the echoic memory having a subserving role to the working memory), there may be an indirect relationship between surgical changes in the evoked potentials and in neuropsychological tests. A relationship might also be present between the surgical changes of the evoked potentials and the surgically resected volume of the brain, if the surgical resection included the evoked potential generators.

Material and methods

2.1 -Control group

The Ethics Committee of the National Hospital for Neurology and Neurosurgery approved the project and both patients and normal volunteers gave their informed written consent according to the Declaration of Helsinki. A control group of 31 normal hearing volunteers was recruited among the staff of the National Hospital, with an age range of 20-49 years (mean 33.4 years, S.D. 6.9). All were right handed and there was a similar proportion of males and females (15 F; 16 M). Data from the normal control group is presented in the Appendix.

2.2 -Patient groups

One hundred and forty-eight patients with temporal lobe epilepsy volunteered for the study. Patients were mostly recruited (from March 1999 to August 2001) from the population attending the Sir Jules Thorn Telemetry department for a pre-surgical assessment. The patients were divided into different groups according to MRI characteristics.

The first group was made up of 98 patients with right (41) or left (55) hippocampal sclerosis on MRI and two patients (A41 and A49) with bilateral hippocampal sclerosis. The subgroup presenting with right hippocampal sclerosis included both subjects with bilateral hippocampal sclerosis (both showing larger hippocampal abnormalities on the right side). This group comprised 25 females and 18 males (n = 43), with a mean age of 34.1 years (S.D. 7.7, range 20-61). Four patients had a left-hand preference and one patient was ambidextrous. Patients with hippocampal sclerosis were identified as group A in tables, but this subgroup will be addressed in the text as the "right hippocampal sclerosis subgroup".

The mean duration of disease for the right hippocampal sclerosis subgroup was 23.6 years (S.D. 11.4, range 6-49). Twenty-eight patients had a history of febrile convulsions, four had a history of cerebral trauma, and three had had meningitis in infancy. Eight patients did not have any previous pathological history. Neurological examination was normal except for six patients (A10, A41, A42, A49, A71, A75) showing mild forms of movement disorders, ranging from essential tremor to ataxia and impairment of fine movements. While 34 of the patients presented only with right hippocampal sclerosis and two had bilateral hippocampal sclerosis, a subgroup of seven presented with additional lesions, summarized in Table 2-1:

Table 2-1. Additional lesions on MRI for patients with right hippocampal sclerosis

Patients	MRI
A5	Right hippocampal sclerosis+ high signal in the left insula
A17	Right hippocampal sclerosis+ cortical dysplasia in the supramarginal gyrus
A42	Right hippocampal sclerosis+ generalized atrophy
A43	Right hippocampal sclerosis+ gliosis in the right frontal lobe
A71	Right hippocampal sclerosis+ cerebellar atrophy + generalized white matter lesion
A75	Right hippocampal sclerosis+ cerebellar atrophy
A92	Right hippocampal sclerosis+ high signal in the inferior part of the internal capsule

Seventeen patients experienced several forms of simple partial seizures with a mean of 43.7 seizures per month (S.D. 70.5, range 1-240). Thirty-seven patients experienced complex partial seizures (mean 20.8 seizures per patient per month, S.D. 51.6, range 2-180). Twenty-one patients experienced generalized seizures with a mean occurrence of 16.5 seizures per month (S.D. 65.0, range 1-3600 per year). The average daily use of anti-epileptic drugs was 2.5, 20 patients using 3 or more anti-epileptic drugs per day.

The subgroup presenting with left hippocampal sclerosis had 32 females and 23 males (n = 55). The patients' ages ranged from 18-62 years, with a mean age of 34.9 years (S.D. 5.4). Three patients were ambidextrous and five patients were left-handed.

This subgroup showed mean disease duration of 25.7 years (S.D. 11.7, range 3-48 years). Twenty-four patients had a previous history of febrile convulsions in infancy while 10 had a previous history of meningoencephalitis, also in infancy. Two patients (A47 and A67) had previous brain vascular events, detected in the MRI. Seven patients had had some form of previous cerebral trauma, but 10 did not have any particular previous pathological history. There was no information regarding the previous clinical history for two patients. Neurological examination was normal except for six patients, whose deficits ranged from a pyramidal weakness (A6, A11) to nystagmus and narrowing of the visual field. Patient A67 presented a bilateral peripheral hearing loss, which was overcome by increasing the intensity of the stimuli used for evoked potential recording.

Forty-one patients presented only with left hippocampal sclerosis on the MRI. Fourteen patients presented with additional lesions, summarized in Table 2-2:

Table 2-2. Additional lesions on MRI for patients with left hippocampal sclerosis (DNET= disembryoplastic neuroepithelial tumour)

Patients	MRI
A3	Left hippocampal sclerosis+ left hemi cerebral atrophy
A4	Left hippocampal sclerosis+ generalized white matter lesion
A6	Left hippocampal sclerosis+ left temporal cortical dysplasia
A9	Left hippocampal sclerosis+ left parietooccipital lobe venous malformation
A11	Left hippocampal sclerosis+ generalised cerebral atrophy
A33	Left hippocampal sclerosis+ cortical damage in the right inferior frontal area
A40	Left hippocampal sclerosis+ generalized white matter lesion
A47	Left hippocampal sclerosis+ left parietal posterior frontal large cystic encephalomalacia
A56	Left hippocampal sclerosis+ generalized white matter lesion
A67	Left hippocampal sclerosis+ left temporal ischemic lesion
A70	Left hippocampal sclerosis+ DNET in the left inferior temporal lobe
A76	Left hippocampal sclerosis+ right parietal lobe ischemic lesion
A81	Left hippocampal sclerosis+ dysplasic lesions in the anterior part of left frontal lobe
A98	Left hippocampal sclerosis+ generalized white matter lesion

Thirteen patients had simple partial seizures ranging from 2 to 900 per month, with a mean of 109 seizures per patient per month (S.D. 243.4). Fifty-one subjects experienced complex partial seizures ranging from 1 to 600 per month, with a mean of 38.5 seizures per patient per month (S.D. 96.7). Eighteen patients had generalized seizures ranging from 1 to 360 per year, with a mean of 1.8 seizures per patient per month (S.D. 5.4). A range of 1 to 4 different anti-epileptic drugs was used, with a mean of 2.3 per patient. Twenty-one patients were using 3 or more anti-epileptic drugs per day.

The second group of patients included 35 with lesions that were not hippocampal sclerosis (19 males, 16 females). Their mean age was 33 years (S.D. 8.5, range 17-55). Four patients were left-handed and one patient was ambidextrous. This group was called group B in the tables, but will be addressed as "non-hippocampal sclerosis subgroup" in the text.

The clinical history of patients in the non-hippocampal sclerosis subgroup had a mean duration of 16.4 years (S.D. 8.6), with a range of 2-40 years. Twenty-three patients had no significant previous pathological occurrences. One patient had a previous history of febrile convulsions in infancy, four patients had a cerebral tumour, and six had had birth problems and/or cerebral trauma during childhood. One patient had a congenital facial malformation.

Neurological examination was normal except for eight patients, whose deficits ranged from pyramidal weakness (B3, B22) to ataxia and nystagmus (B12, B15, B20, B25, and B32). Patient B21 had a previous surgical excision of a left parietal abscess and complete peripheral hearing loss on the left. Table 2-3 presents the MRI conclusions for group B patients:

Table 2-3. MRI results for group B patients (AVM = arteriovenous malformation)

	Patients	MRI
Group B-L	B1	Left temporo-parietal cortex encephalomalacia
Group B-L	B2	Left dysplasic lesion anterior to the brainstem
Group B-L	B3	Left inferior temporal gyrus DNET (mid portion)
Group B-L	B4	Left temporal low grade tumour / calcified angioma
Group B-L	B7	Left temporal lobe AVM
Group B-L	B8	Left temporal cavernous angioma
Group B-L	B9	Left temporal lobe partial excision
Group B-L	B12	Left frontal operculum focal atrophy
Group B-L	B15	Left superior and middle temporal gyri cortical dysplasia
Group B-L	B19	Left parahippocampal gyrus DNET
Group B-L	B21	Brain damage in the left superior and middle frontal gyri,+?residual meningioma
Group B-L	B22	Left tentorial meningioma
Group B-L	B23	Left temporal vascular tumour
Group B-L	B28	Left posterior temporal lobe DNET
Group B-L	B29	Left temporal lobe DNET involving the uncus
Group B-L	B35	Left posterior hippocampal DNET–medial temporal area
Group B-R	B11	Right amygdala dysplasic lesion
Group B-R	B13	Right hippocampus cavernoma
Group B-R	B14	Right calcarine fissure cortical dysplasia
Group B-R	B17	Right anterior temporal lobe DNET
Group B-R	B18	Right inferior frontal gyrus DNET
Group B-R	B5	Right temporal lobe brain damage (anterior portion) secondary to TCE
Group B-R	B24	Right choroidal fissure cyst next to the hippocampus
Group B-R	B25	Right mesial temporal area DNET
Group B-R	B26	?Angioma in the right supplementary motor area
Group B-R	B27	Poorly defined lesion R occipital lobe, ?cortical dysplasia
Group B-R	B33	Right cavernoma in the colateral sulcus of the temporal lobe
Group B-R	B34	Right posterior frontal region DNET

Group B-BB B6	Generalized white matter lesion
Group B-BB B10	Right frontal tumour and generalized white matter lesion
Group B-BB B16	Bilateral white matter lesion
Group B-BB B20	Frontal lobe white matter lesion
Group B-BB B30	Bilateral white matter lesion adjacent to lateral ventricle
Group B-BB B31	Brain damage both in the left frontoparietal and right frontal region
Group B-BB B32	Bilateral polymicrogyria, mostly frontal

Patients were allocated to three different subgroups according to their MRI results. The first subgroup had 16 subjects with left side lesions (called "left lesions not hippocampal sclerosis"), the second subgroup had 12 subjects with right side lesions (called "right lesions not hippocampal sclerosis") and the third subgroup had seven patients with bilateral lesions (called "bilateral lesions not hippocampal sclerosis").

Eleven patients had simple partial seizures ranging from 3 to 150 per month (mean 53.3 per patient per month, S.D. 87.7). Twenty-six patients had complex partial seizures (2-300 per month, mean 78.4, S.D. 182.6). Twenty-three patients presented with generalized seizures, with a range of 1-720 per year (mean 4.0 per patient per month, S.D. 10.5). On average, patients were medicated daily with 2.1 anti-epileptic drugs, ranging from 1-3. Twelve patients were medicated with more than 2 anti-epileptic drugs per day.

A third group consisted of 15 patients (5 females, 10 males) with complex partial epilepsy of probable temporal lobe origin, but with normal MRI. The mean age was 34.6 years (S.D. 9.6, range 20-50). Mean disease duration was 18 years (S.D. 10.7, range 1-36). Three patients had a history of perinatal or childhood trauma, two had a history of febrile seizures and two had episodes of meningoencephalitis in childhood. Neurological examination was normal except for three patients who presented nystagmus (C10, C14, C16) and an acquired plexopathy (C3). Three patients were left- handed.

Six patients had simple complex seizures, with a mean of 351 seizures per patient per month (S.D. 549.3, range 1-1200). Fourteen patients had complex partial seizures with a mean frequency of 10.1 per month, (S.D. 16.1, range 2-30). Six patients had generalized seizures with a mean of 0.4 per month (S.D. 0.6, range 0-2 seizures per patient per month). The mean daily use of anti-epileptic drugs was 2.3 per patient, ranging from 1-4. Four patients were medicated with more than 2 anti-epileptic drugs per day.

2.3- Study design

The recordings of the control group were performed in a quiet environment, in the evoked potential laboratory. The subjects sat in an armchair and read a book for the duration of the test, which was approximately 15-20 min. The only instruction given was for the subjects to relax and read continuously, with no verbal response required. One hundred and forty-eight patients suspected of having hippocampal sclerosis were recorded in the Sir Jules Thorn Telemetry department for a pre-surgical assessment using the same machines and stimuli as the normal control group. Patients were assessed at the beginning of a five-day stay, while still using their previous medication.

a) Pre-surgical group

In order to test the first hypothesis, that auditory evoked potentials might be affected according to the location of the epileptic focus, all pre-surgical responses from these patients were compared with the responses from the control group. Data from each patient were collected from the patient's notes and the following values were recorded: age, disease duration (years), MRI results, type and frequency of seizures per month and number of anti-epileptic drugs used per day.

b) Surgical group

In order to test the second hypothesis, that auditory evoked potentials might be affected by the surgical resection, a subgroup of 42 patients with hippocampal sclerosis and other types of lesions was assessed before and after surgery, performed 6-9 months after the first test. This entailed the evaluation of the post-surgical responses in comparison with the pre-surgical responses. Normal data was obtained from a subgroup of the control group (15 subjects, 7F; 8M, mean age 33.5 years, SD 7.8), that was recorded for a second time in the same circumstances, after 6-12 months, in order to assess test/retest variability in the waveform amplitude and latency and to reproduce as closely as possible the recording conditions of the surgical patients group.

Surgical patients were assessed using evoked potentials, once in the Telemetry ward, at the beginning of a five-day stay, while still using the previous medication, and a

second time 3-6 months after surgery; this time the evaluation was performed in the evoked potential laboratory.

Three surgical subjects did not reply to the request for a second evoked potential evaluation, and one patient was omitted due to technical problems during the second recording. Forty-two patients, 22 females and 20 males, with a mean age of 34.6 years (S.D. 8.6, range 20-61years) composed the surgical group. Mean duration of disease was 22.2 years (S.D. 11.0, range 6-50). Three patients were left-handed, 2 were ambidextrous. Seventeen patients had left hippocampal sclerosis, 19 patients had right hippocampal sclerosis and 6 patients had other types of cerebral lesions described in Table 2-4 (non-hippocampal sclerosis). In the subgroup with right hippocampal sclerosis, two patients were left-handed and one patient was ambidextrous. In the subgroup with left hippocampal sclerosis, one patient was left-handed and one patient was ambidextrous.

Table 2-4. MRI results for surgical group (non-hippocampal sclerosis)

Patient	MRI
B5	Right sequelar lesion in the anterior portion of temporal lobe
B7	Left temporal lobe AVM
B8	Left temporal cavernous angioma
B13	Right hippocampus cavernoma
B18	Right inferior frontal gyrus DNET
B19	Left parahippocampal gyrus DNET

Fifteen patients presented with simple partial seizures (mean 57.9 per patient per month, S.D. 77.0, range 2-240). Thirty-six patients presented with complex partial seizures (mean 13.6 per patient per month, S.D. 15.8, range 1-60). Fifteen patients presented with secondary generalized seizures (mean 5.8 per patient per month, S.D. 2.7, range 0-60). Patients were medicated with a mean of 2.4 anti-epileptic drugs (range 1-4), 21 being medicated with more than 2 anti-epileptic drugs per day.

All patients were selected for surgery after Telemetry, MRI, neuropsychiatry and neuropsychological evaluation. Surgery was performed within 6-12 months of the first evoked potential recording and involved the resection of the lateral temporal neocortex, the anterior hippocampus and the amygdala (3.5 to 4 cm. of the lateral neocortex, 3 cm. of the hippocampus), or resection of the lesion (in patients B5, B7, B8, B13, B18 and B19).

All patients were still using the same medication as before surgery when tested for the second time. After surgery, only two patients with right hippocampal sclerosis still presented seizures (A29 and A77), A29 reporting a lesser number than before. Two patients (A22, A37) were clinically depressed and one patient (A5) mentioned difficulties following a sound source when several sounds were present simultaneously (streaming).

Only two patients with left hippocampal sclerosis (A2, A7) maintained seizures after surgery, although less frequently for patient A7. Patient A2 reported periods of confusion after surgery. Mood swings and emotional liability were mentioned by five patients (A27, A39, A52, A58, A59).

Only three patients without hippocampal sclerosis (non-hippocampal sclerosis subgroup) maintained seizures after surgery: B7 only had simple partial seizures, B8 maintained complex partial seizures but less than previously, B5 had an equal number of seizures. Two patients, B7 and B13, reported difficulty with sound streaming post-surgically.

2.4 -Evoked potentials - recording procedures

Patient groups with right and left hippocampal sclerosis, with non-hippocampal sclerosis and with normal MRI were recorded using electrodes placed with collodion at the Telemetry ward. For studies performed in the evoked potential laboratory (controls and post-surgical patients), an abrasive gel was applied on the scalp ensuring good electrical contact between the skin and the Ag/AgCl disc electrodes, which were attached to the head with EEG paste (electrolyte). All the impedances of the recording electrodes were below 5KΩ and within 1KΩ of one another. The recording electrodes were placed according to the 10/20 system on the midline at Fz, Cz and Pz and on the right and left hemispheres at locations: Fp1, Fp2, F3, F4, F7, F8, C3, C4, T3, T4, T5 and T6. The reference electrode was placed just above the inion. The ground was placed at any location on the scalp. Finally, a single electrode was placed on the nose, in order to allow the other electrodes to be referred to it off-line and to reproduce the more frequent montage to obtain the MMN as seen in the literature.

2.4.1 -Recording apparatus

A Yamaha MU10 Tone Generator controlled by an IBM compatible Daewoo Laptop PC created the stimuli. The software used to construct and play stimulus sequences

was Midisoft Recording Studio (Diamond Computer Systems Inc.) plus Cubasis (Steinberg Soft and Hardware Gmbh). The left and right output channels were split in order to use one channel for the stimulus (presented binaurally through headphones) and the other to trigger the recording apparatus. The transformation of sound into digital TTL trigger pulses was performed using a tone to pulse converter created in the engineering department of the Department of Clinical Neurophysiology.

The recording apparatus comprised an IBM compatible Gateway 2000 lap-top PC running Signal software (CED, Cambridge) which controlled a CED 1401 plus A/D converter and CED 1902 amplifiers. The recording bandwidth was 1Hz to 200Hz with an averaging epoch of 500 ms. and an A/D conversion rate of 1 KHz. The pre-stimulus baseline period was 100 ms.

2.4.2 -Sound stimulus

The choice of the three conditions was performed in order to assess auditory responses to discontinuous complex tones (Onset) that produce the classical N1/P2 complex, to continuous complex tones changing spectrally (Frequency Change) and to continuous complex tones changing in both spectral and temporal characteristics (Mismatch).

All sounds had a smooth onset and offset with a rise time of approximately 10 ms. established by examination of their waveforms, (this was also done to establish the precise temporal relationship between stimulus and trigger) and approximately 20 ms. of overlap between elided tones (Figure 2-1 and 2-2).

The tones were played in "clarinet" timbre, chosen on account of its unexaggerated onset and subsequent steady intensity and pitch. The sound spectrum was analyzed using a fast A/D converter and associated software (Pico Technology, Cambridge, UK).

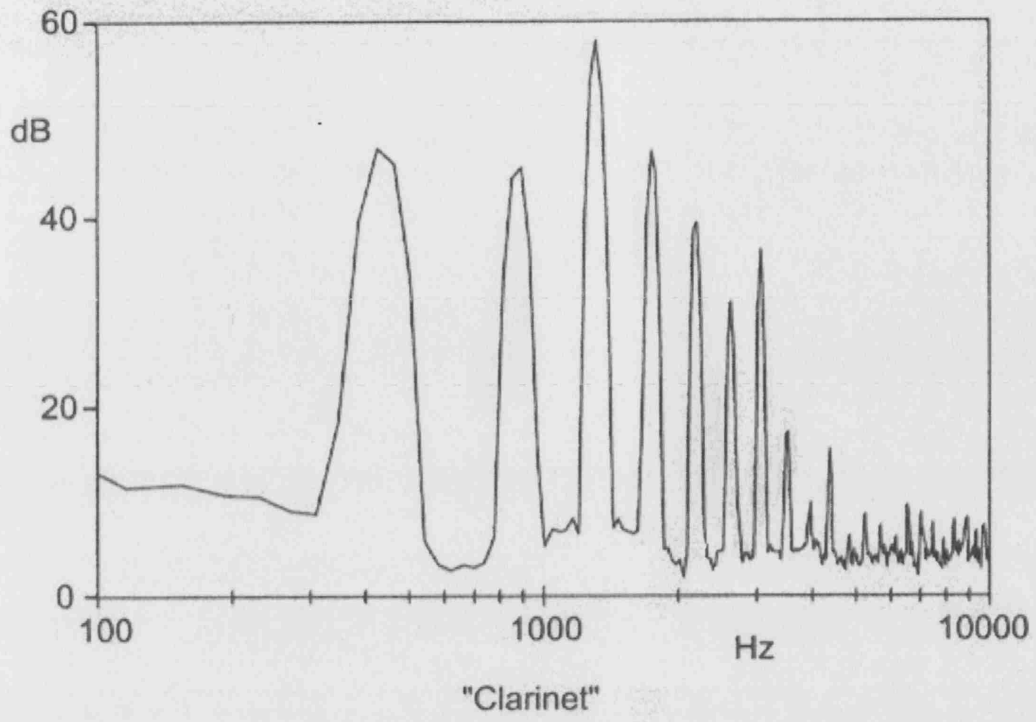

Fig.2-1. Sound spectrum of the "clarinet" tone with a fundamental frequency of 440Hz (A4 in musical terminology).

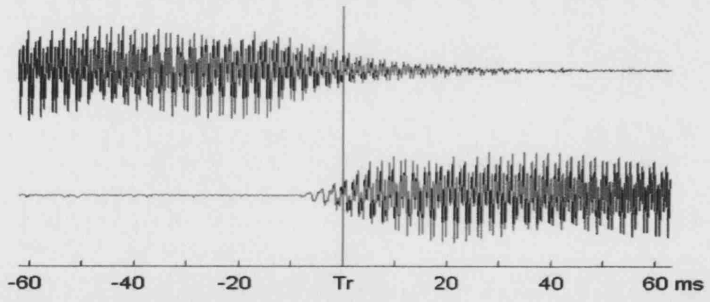

Fig.2-2. Succession of two tones, showing overlapping of waveforms.

The baseline fundamental frequency was 440Hz (A4 pitch) and the intensity was 45-50 dB above threshold. Three different stimuli (tone patterns) constituted the experimental procedure: the first one, named "Onset" – was a sequence of tones (A4), presented out of silence, each with a duration of 1 s. and followed by a gap of 1 s.

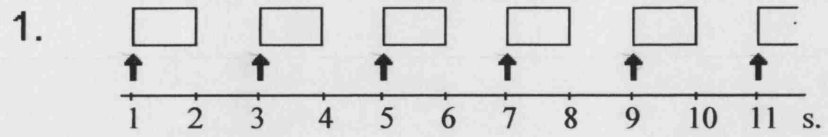

Fig.2-3. Onset stimulus

The second stimulus was named " Frequency Change" and was produced by two tones (A4 and B4, fundamental frequencies of 440Hz and 494Hz respectively), alternating every two seconds with no gap.

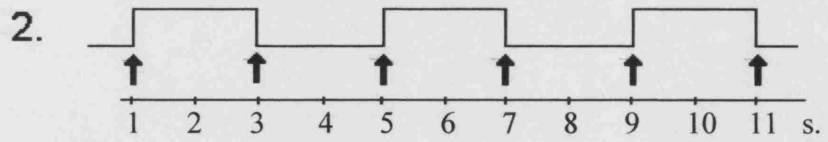

Fig.2-4. Frequency Change stimulus

The third sequence of tones was called "Mismatch" and was composed of a repeating pattern of oscillations between A4 and B4, produced at a rate of 16 notes/s. for a duration of 2 s., coming to rest on a steady tone (B4) for 1 s.

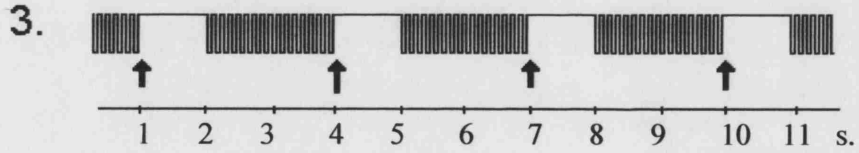

Fig.2-5. Mismatch stimulus

Each stimulus sequence had 50 triggers, one with every note in Onset, one with every change in Frequency Change. In Mismatch, the trigger was placed at the end of the 16 Hz oscillations, at the moment when the next change in pitch was expected and did not occur. Each run then included the same number of responses and the final average, consisting of three runs for each condition, had the same number of triggers for each condition (150).

Final average waveforms were processed through a digital notch filter in order to remove contamination by extraneous frequencies in the 50 Hz region. Fig. 2-6 shows an example of average waveforms before and after filtering.

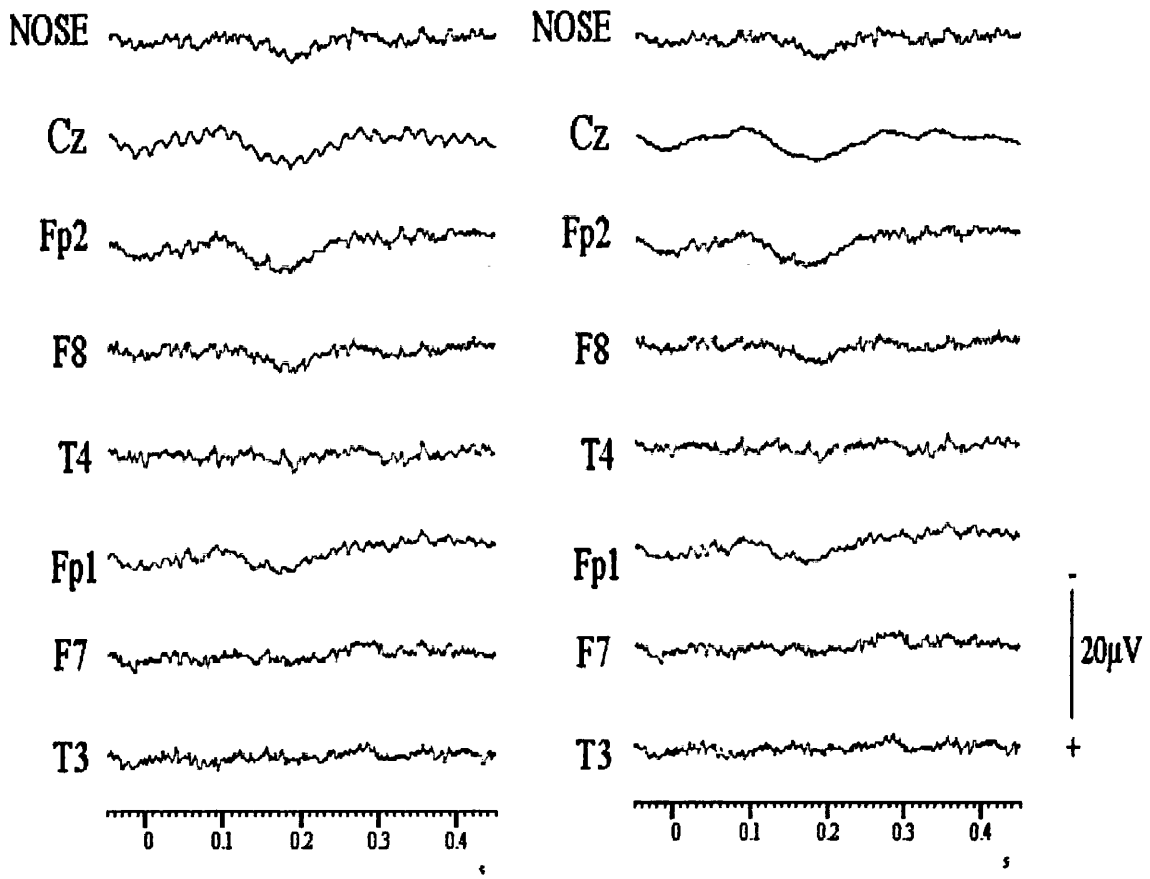

Fig.2-6. Mismatch responses from a normal control subject (NC 26). A 50Hz notch filter was applied and the filtered waveform is presented in the right side, reducing the 50 Hz components.

2.4.3 -Waveform evaluation

In each condition, a negativity at around 100 ms. (N1) and a positivity at around 200 ms. (P2) were observed. In the Onset and Frequency Change condition a negative / positive complex (the T-complex, described by Wolpaw and Penry (1975)) was identified at the temporal electrodes (T4, T6 on the right and T3, T5 on the left) in most of the subjects.

N1 and P2 amplitude and latency values were evaluated at frontal electrodes (F4 and F3) and central electrodes (C4, C3) in all conditions. The T-complex latency was evaluated at temporal electrodes (T4 and T3) in the Onset and Frequency Change condition. Latency was measured to the peak of each component; amplitude was measured relative to a cursor placed on the pre-stimulus baseline. Normal latency limits were obtained by adding and subtracting 2.5 standard deviations from the mean. Differences between left and

right electrodes were calculated by subtracting the left latency from the right latency, and normal limits were obtained by the mean +/- 2.5 S.D..

Due to their non-Gaussian distribution, amplitude values were converted to logarithms, from which normal amplitude limits were obtained by adding and subtracting 2.5 S.D. from the mean and subsequently reconverting to absolute values. An index of asymmetry was obtained by subtracting the left waveform amplitude from the right waveform amplitude and dividing the result obtained by the sum of both amplitudes (right and left). Normal limits for this index were defined by the mean +/- 2.5 S.D.

Recordings from pre-surgical patients were evaluated in relation to the normal limits defined in the control group.

As described before, a test/retest variability measure was obtained for amplitude and latency with the sequential measurements from 15 normal controls. Latency normal limits for test/retest variability were defined as the mean +/- 2.5 S.D. resulting from the subtraction of the latency obtained at the second recording from the latency obtained at the first. Amplitude test/retest variability was assessed by subtracting the amplitude of the second recording from the amplitude of the first recording and dividing the result by the sum of the first and the second recording amplitudes. Normal limits were defined by the mean +/- 2.5 S.D.

For surgical patients, each post-surgical waveform was evaluated according to the normal limits defined in the control group. The final number of abnormalities was compared with those found in the pre-surgical evaluation. Post-surgical test/retest changes were also evaluated applying the imits obtained from the normal control group. The pattern of observed changes allowed the classification of subjects as improving, deteriorating or mixed. The correlation of post-surgical test/retest changes with neuropsychological changes was assessed, as well as the correlation of post-surgical test/retest changes with the resected surgical volume.

2.5 -Neuropsychology

Surgical patients were evaluated with a battery of neuropsychological tests used routinely by the Neuropsychological Department of the National Hospital for Neurology and Neurosurgery (eg: Baxendale et al., 1998). The measures of memory employed were the Story Recall, List Learning, Figure Recall and Design Learning sub-tests from the Adult Memory and Information Processing Battery (AMIPB) (Coughlan, A, 1985). The

AMIPB has been standardized in a British sample. The tests were performed before and after surgery, with a similar delay as the re-testing of the auditory evoked potentials, the second test roughly at the same time as the second AEP recording.

2.5.1 -Verbal memory tests

Measures of verbal memory have been shown to be sensitive to pathology in, and following surgery of, the left (dominant) temporal lobe, with tests of learning and recall being particularly susceptible to mesial temporal pathology (Lee et al., 2002) and recognition tests being more sensitive to damage in the lateral temporal structures (Baxendale et al., 1997).

The Story Recall Test is designed to assess immediate registration of verbal information and retention over time. The subject is read a short story and has to recall it immediately as well as after a thirty-minute delay. The scores obtained are the number of ideas (maximum 60) recalled on these two occasions and also the percentage of ideas retained (delayed score/immediate score * 100).

The List Learning test assesses rote learning of verbal information and susceptibility to interference. In the List Learning test, a list of 15 words is presented five times, and after each presentation the patient is asked to repeat the list. A second list is presented once and recall is tested. Following this the subject is asked to recall the original list. A total score of correct responses over the five initial trials is recorded (max = 75) and also the total number of false positives (intrusions). The total number of items recalled from the second list and the total from the original list after the distracting list are also recorded.

In the Word Recognition test the patient is presented with fifty single words for three seconds each and subsequently has to select from fifty pairs of words the item they have been previously shown. The score is the total number of words correctly identified (max = 50).

2.5.2 -Visual-spatial memory tests

Measures of spatial memory have been shown to be sensitive to pathology in, and following surgery of, the right (non-dominant) temporal lobe with tests of learning and recall being particularly susceptible to mesial temporal pathology (Baxendale et al., 1998, Lee et al., 2002) and recognition tests being more sensitive to damage in the lateral

temporal structures (Baxendale et al., 1997). Findings in the research literature have been less consistent and striking than those for verbal memory and left temporal pathology.

The Figure Recall test assesses the immediate registration of visual information and retention over time. The subject has to copy a complex 2-D figure and reproduce it immediately and thirty minutes later. The scores obtained are percentages retained immediately and following the delay (max 100%) and the percentage retained (delayed/immediate *100).

The Design Learning task assesses the rote learning of visual information and susceptibility to interference. In the rote learning phase the subject attempts to learn a small nine line design over five trials. Susceptibility to interference is assessed by requesting recall of this original design following a one trial attempt to recall a new design. A total score of correct responses over the five initial trials is recorded (max = 45) and also the total number of false positives (intrusions). The total number of items recalled from the second design (max = 9) and the total from the original design (max = 9) after the distracting design are also recorded.

Correlation tests between post-surgical changes in evoked potentials (obtained by the latency difference between the second and the first recording and the amplitude ratio of the first and the second recording) and post-surgical changes in Neuropsychological scores were performed. In order to decrease the number of correlations and the corresponding danger of type I error, a score, obtained from the difference between pre- and post-surgical neuropsychological sub-tests, was calculated for each group of sub-tests. A final mean value was obtained for each group of tests.

For each stimulus condition (Onset, Frequency Change, Mismatch) Pearson's Correlation test was performed between a dependent auditory evoked potential variable (N1 recorded at the right and left electrodes, P2 recorded at the right and left electrodes) either in amplitude or in latency and each of 5 grouped neuropsychological test scores. Due to the large number of correlations performed, it was decided that in order to minimise the risk of type I error the accepted p value should be equal to or less than 0.005.

2.6 -MRI measurements

MRI images were obtained pre- and post-surgically, as part of the normal clinical assessment. The images were acquired on a 1.5-T GE Signa Horizon scanner, using an inversion recovery prepared SPGR volume acquisition sequence in the coronal plane

(TI/TR/TE= 450ms/15ms/4.2ms; flip angle, 20 degrees; number of excitations, one; number of partitions, one, 124 slices; matrix, 256*192; field of view, 24*18caudo medial). Slice thickness was 1.5 mm and the scan time was 6 min and 56s.

The analysis of temporal lobe resections was done using a standardized method reported by Moran et al. (1999) in which the resected volumes are manually delineated in the pre-operative and post-operative MRI images. Both images were displayed simultaneously using a co-registration system (eg: Lemieux et al., 1998), that compensates for varying patient position and orientation in the field of view in serial imaging. The resection tissue was delineated, commencing in the most posterior slice showing lack of tissue due to resection, and continuing anteriorly until a slice was encountered with no evidence of surgical procedures. The resected tissue was manually delineated in every alternate 1.5mm slices using a mouse driven cursor, with the preoperative scan as a reference. Within each slice the trace area was automatically calculated by multiplying the number of pixels within the trace by the pixel area (0.9375*0.9375 mm^2). The total resected volume was obtained by multiplying the sum of all traces by twice the slice thickness (2*1.5mm).

2.7 -Statistical methods

A Univariate Analysis of Variance was used to examine differences in seizure frequency, disease duration and number of anti-epileptic drugs among the pre-surgical subgroups of patients (hippocampal sclerosis, non-hippocampal sclerosis and normal MRI). A Multivariate Analysis of Variance was used to compare pre-surgical amplitude and latency for N1 and P2 between the normal control group and each patient subgroup.

The χ^2 test was used to investigate the association between normal and abnormal responses from each group of patients and to evaluate differences for this distribution between the groups. The Student T-test was used to compare amplitude and latency within each patient's subgroup.

For the surgical group of patients, Repeated Measures Analysis of Variance was performed in order to compare pre- and post-surgical values of N1 and P2 latency/ amplitude. The incidence of abnormalities present in each subgroup of surgical patients was compared using the χ^2 test.

The Wilcoxon signed rank test was used to compare mean number of abnormalities per patient before and after surgery.

Pearson's Correlation test was used to examine the association between post-surgical changes in evoked potential values and post-surgical changes in Neuropsychological mean scores. Pearson's Correlation tests were performed between the resected surgical volume calculated as described before, and surgical changes in evoked potentials, obtained by the latency difference between the second and the first recording, and the amplitude ratio of the first and the second recording.

Tests were performed using the SPSS 9.0 software version, from SPSS Inc.

Results

3.1 Control group data

It was proposed to analyse ON1/OP2, CN1/CP2 and MN1/MP2 in a large group of normal controls with the objective of finding normal limits (mean +/-2.5 S.D.) for each waveform. This delimitation of normal limits, applied to the data of each patient, was intended to detect changes of each patient waveform in terms of amplitude and/or latency, inter-hemispheric latency differences and amplitude ratios. It was also intended to see if the underlying pathology was producing ipsi- or contralateral abnormalities. Normal limits and mean values of the control group are presented in the Appendix.

Figure 3.1 presents the Onset response of a normal control subject:

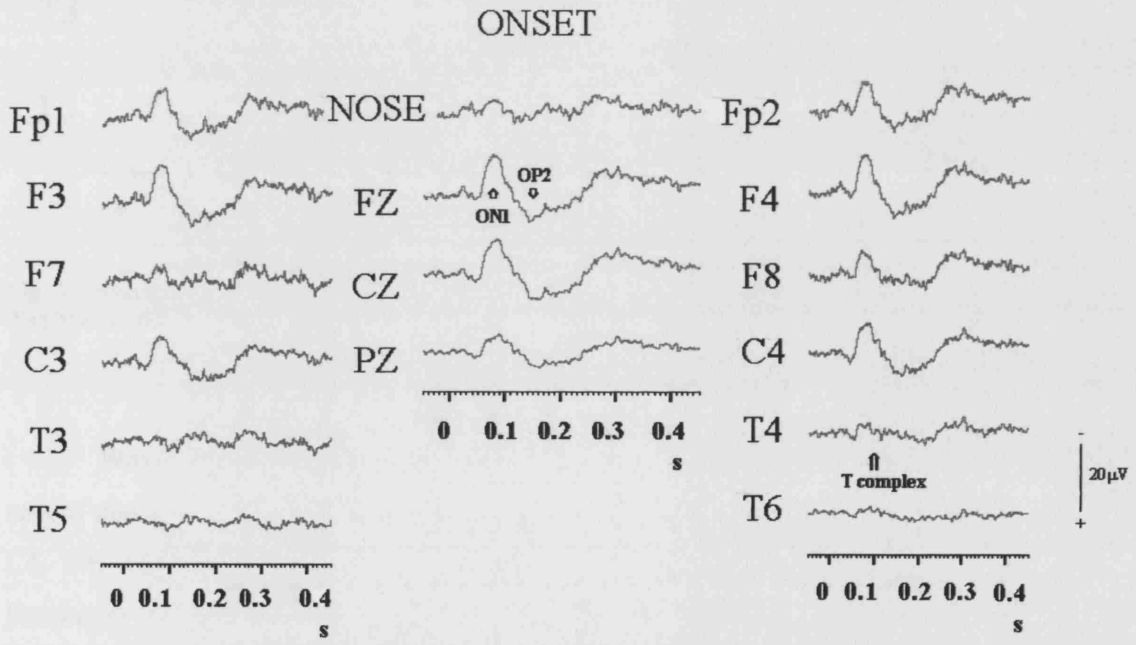

Fig. 3.1 Average Onset responses for a normal control subject (n9). N1 and P2 are largest in amplitude at fronto-central electrodes and the T-complex is doubtfully present at temporal electrodes.

Figure 3.2 presents the average waveforms of the 31 normal subjects for the Onset condition.

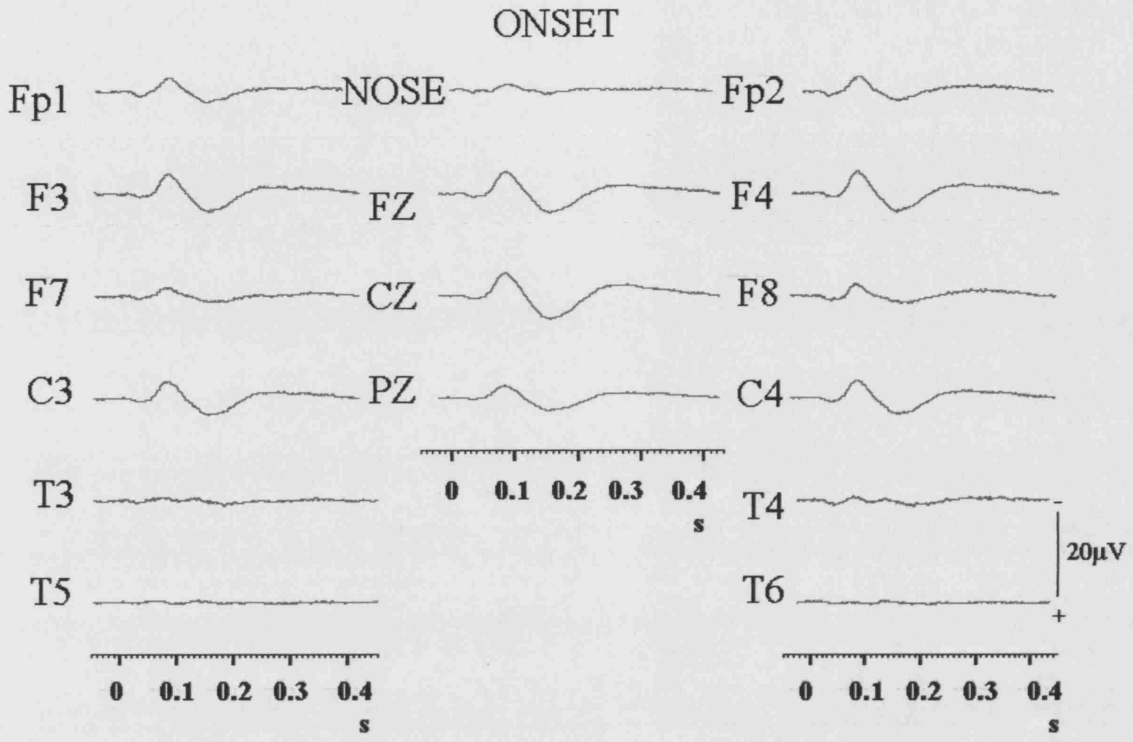

Fig. 3.2 Average responses of the 31 normal controls for the Onset condition. N1/P2 maintain a fronto-central distribution, the T-complex is more prominent at right-sided electrodes.

Waveforms were analysed in each subject and in each condition for three different sets of electrodes: midline electrodes (Nose, Fz, Cz and Pz), right electrodes (Fp2, F4, F8, C4, T4, T6) and left electrodes (Fp1, F3, F7, C3, T3, T5). Latency values for Onset, Frequency Change and Mismatch waveforms were evaluated at Fz, F4 and F3 and are presented in the Appendix.

Latency differences were calculated between right (F4) and left (F3) electrodes. Paired t–tests comparing right and left side latency for ON1 and OP2, CN1 and CP2, MN1 and MN2 in the normal control group were not significant ($p<0.005$). Mean values and normal limits for inter-hemispheric latency differences for Onset, Frequency Change and Mismatch are presented in the Appendix.

Amplitude values were obtained for each channel, measured from the pre-stimulus baseline. In order to normalise their distribution, amplitude values were first converted to logarithms, from which the mean and standard deviation values were obtained. Anti-

logarithms were then used to calculate normal limits. Amplitude limits could not be derived at some electrodes because in some subjects, at N1 and P2 latency, the response obtained at these electrodes did not have the appropriate polarity; hence logarithms could not be obtained. Amplitude values for Onset, Frequency Change and Mismatch were obtained at Fz, Cz, Pz, F4, C4, F3, and C3 and are presented in the Appendix. T-tests comparing amplitude values for the right and left electrodes for each condition were not significant ($p<0.005$).

In order to quantify differences in amplitude between right- and left-sided electrodes, two pairs of electrodes (F4, F3) and (C4, C3) were selected. The expression: (x4-x3) /(x4+x3), where x4 is the amplitude at F4 or C4 and x3 is the amplitude at F3 or C3, was applied to obtain a ratio value, used to define normal limits. Note that the range of this ratio is from –1 when the amplitude at x4 is zero to +1 when the amplitude at x3 is zero. Mean inter-hemispheric ratio values and normal limits for Onset, Frequency Change and Mismatch amplitude are also presented in the Appendix.

As for Onset, Frequency Change waveforms were evaluated for amplitude and latency in each subject. Figure 3.3 shows the Frequency Change average response from a normal subject (n9).

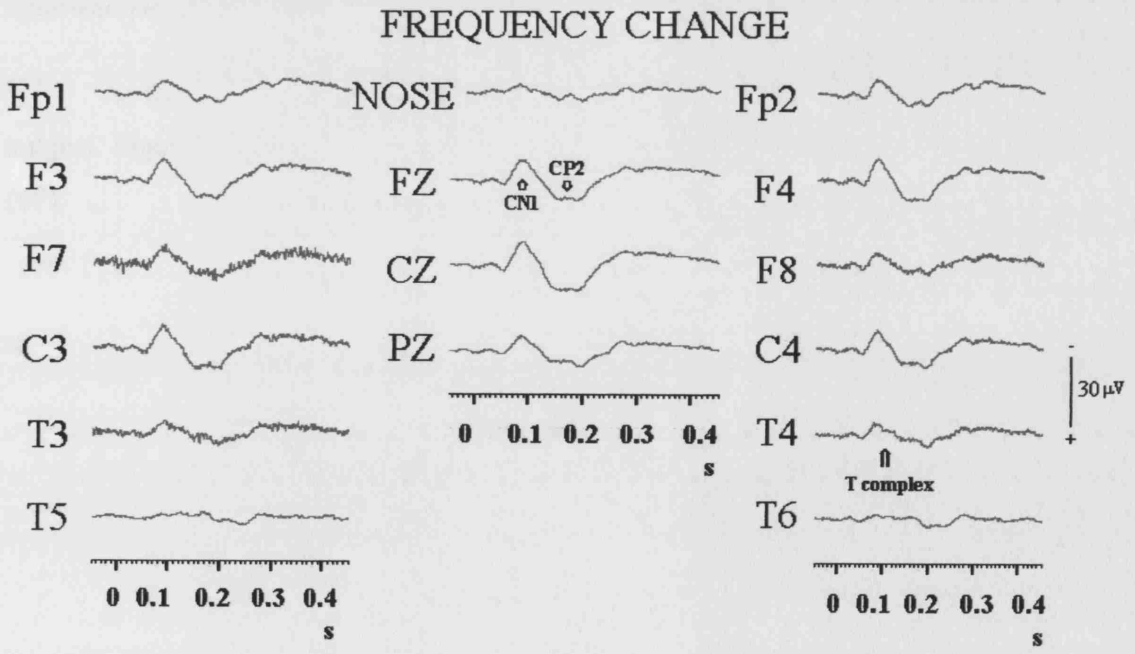

Fig. 3.3 Evoked potentials to Frequency Change in a normal subject (n9). CN1/CP2 show largest amplitudes at fronto-central electrodes and the T-complex is probably present at temporal electrodes bilaterally.

Figure 3.4 shows the Frequency Change average responses from the normal control group.

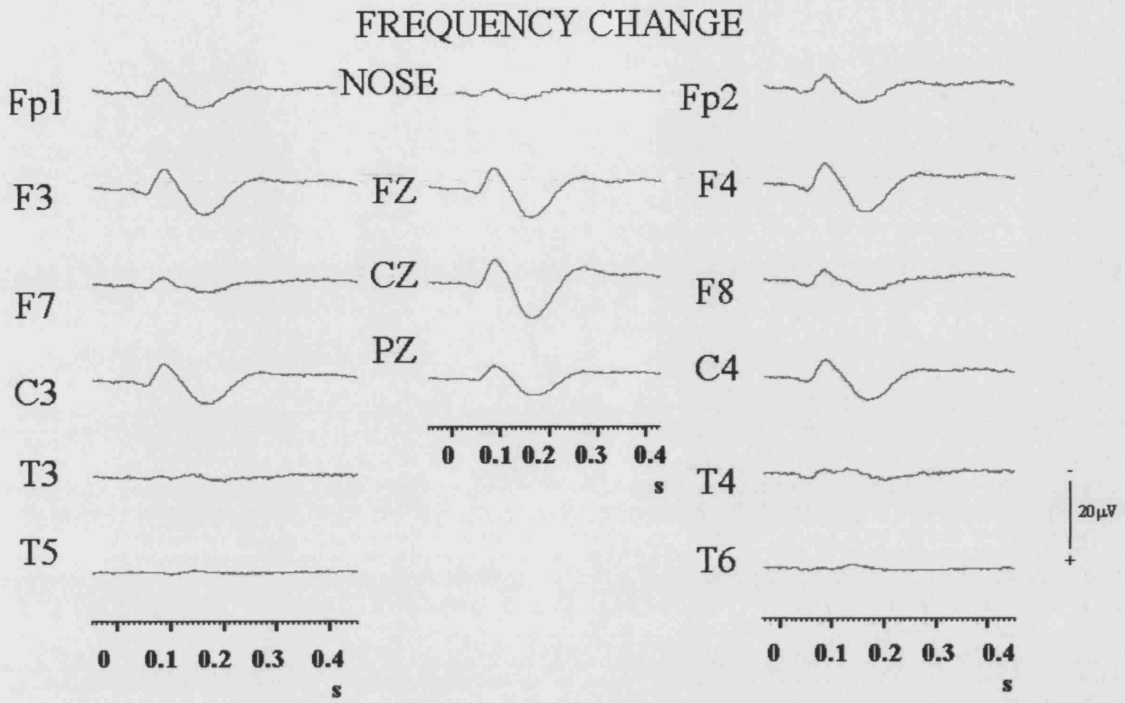

Fig. 3.4 Average evoked potential response of 31 normal controls to Frequency Change. The T-complex is again more prominent at right-sided temporal electrodes

As for Onset and Frequency Change, Mismatch waveforms were evaluated in each subject. Figure 3.5 shows the Mismatch average responses from a normal control subject (n9).

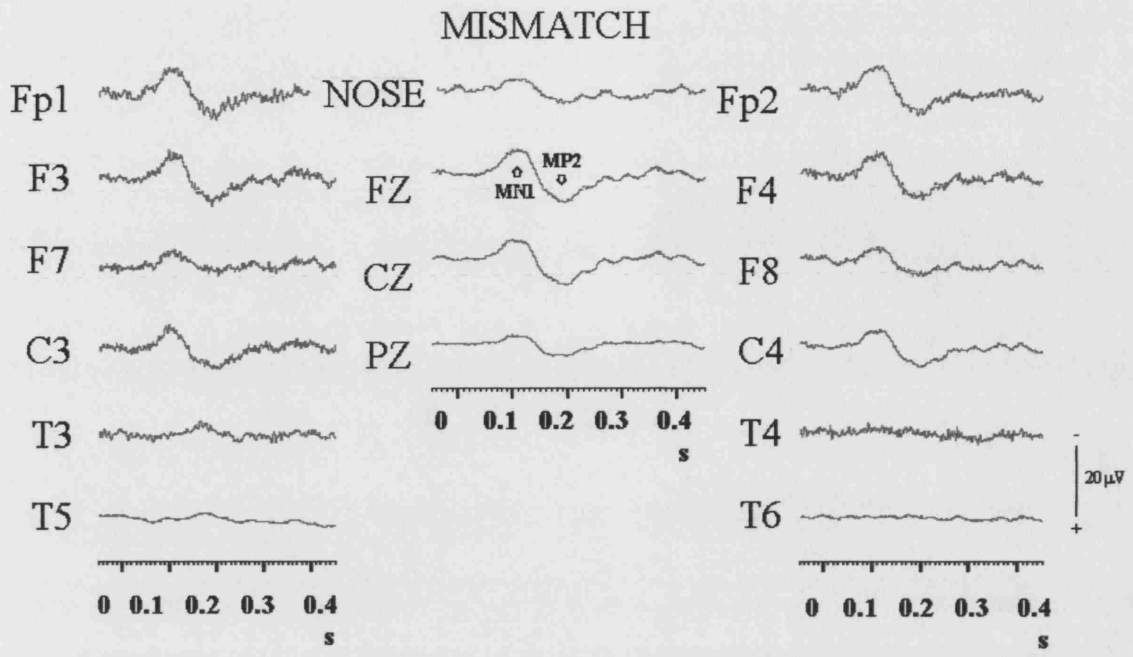

Fig. 3.5 Mismatch responses from a normal control subject (n9). Responses are largest at fronto-central electrodes. T-complex is absent at right electrodes and possibly present at left electrodes.

Figure 3.6 shows the Mismatch average responses from the normal control group.

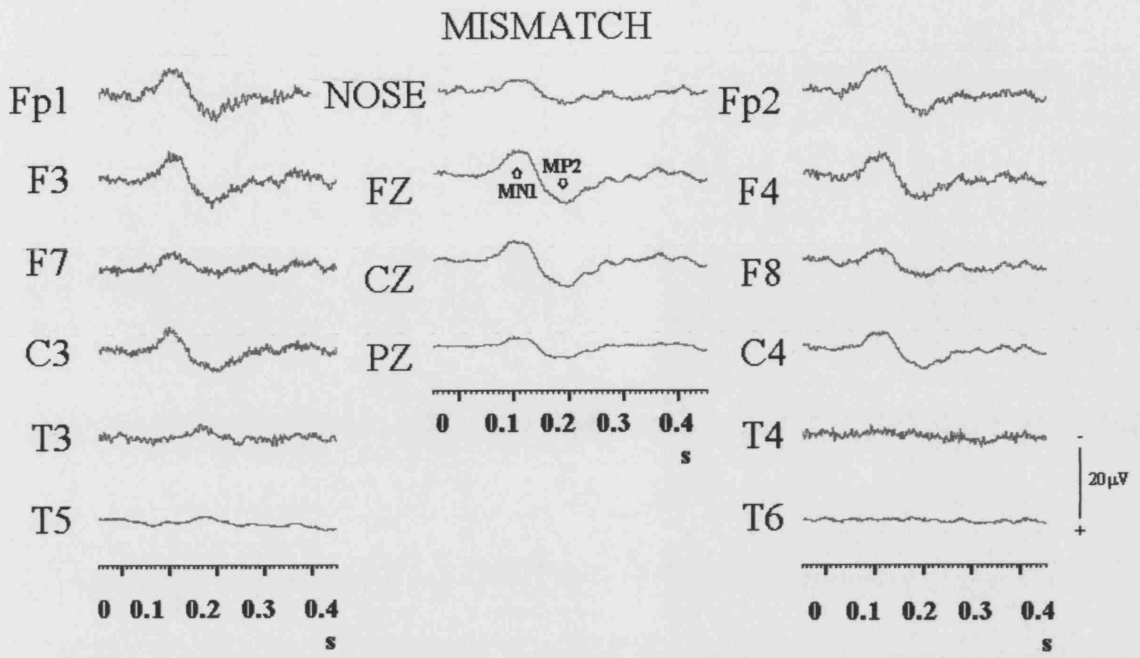

Fig. 3.6 Average responses of the 31 normal controls for the Mismatch condition. MN1/MP2 responses are largest at Fz. No T-complex is evident at temporal electrodes.

3.1.1 The T- complex

Figure 3.7 shows the group mean waveforms at the temporal electrodes for the three conditions:

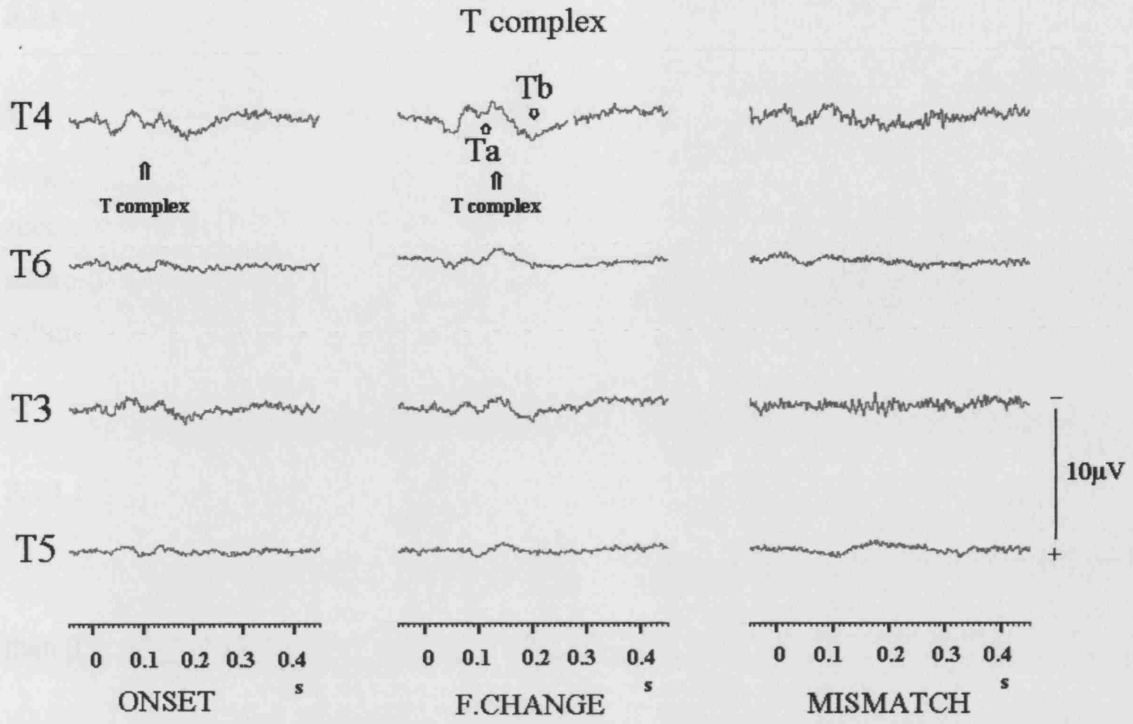

Fig. 3.7 Average waveforms of the 31 normal controls at temporal electrodes for the three conditions

Onset T-complex latencies had a mean value of 141.7 (S.D.=18.1) for Ta and 201.1(S.D.=23.8) for Tb at the right temporal electrodes. Frequency Change T-complex latencies had a mean value of 143.4 (S.D.=17.2) for Ta and 203.3 (S.D.=21.6) for Tb at the right temporal electrodes. Corresponding components were not definitely identified in the Mismatch responses of the normal control group.

For the Onset response, the T-complex was considered to be present on the right side in 19 subjects and on the left side in 15 subjects. Eleven subjects had bilateral responses. Limits for latency and amplitude were not used for patient evaluation since the potential was present in less than 75% (23) of the normal subjects tested.

For the Frequency Change condition, the T-complex was considered to be present in 27 subjects on the right and in 18 subjects on the left. Hence, T-complex amplitude was not used for derivation of normal limits, due to its absence in several normal subjects. Only the latency limits of the right-sided Frequency Change T-complex were used for evaluation of patients. Mean values and normal limits are presented in the Appendix.

3.2 Pre-surgical evaluation

A total of 148 patients with temporal lobe epilepsy were recorded during pre-surgical assessment in the Telemetry Unit. The patients were divided into four subgroups according to MRI data: a subgroup of 98 patients with right (43) or left (55) hippocampal sclerosis, a subgroup of 35 patients with other types of temporal lobe lesions, and finally a subgroup of 15 patients with no observable lesions on the MRI.

3.2.1 Statistical comparison of pre-surgical patient subgroups

Due to the large number of comparisons performed in each group, a p value of less than 0.005 was chosen, in order to reduce type I error.

Univariate ANOVA tests between the four subgroups of patients evaluating "number of seizures/month" for each type of seizure and "number of anti-epileptic drugs/day" did not show any significant differences. A significant difference was found for "years of disease" ($F(2,139)=7.8$, $p=0.001$), the subgroups with hippocampal sclerosis showing a mean value greater than the other two subgroups of patients.

In order to compare the number of abnormal auditory evoked potential components per patient in each subgroup, abnormalities for N1 at the right (N1R) and left electrodes (N1L), abnormalities of P2 at the right (P2R) and left electrodes (P2L) were evaluated for Onset, Frequency Change and Mismatch. Abnormalities were also evaluated for T-complex latency at the right electrodes for Frequency Change. The incidence of abnormal components per subject in the normal control group was obtained.

Table 3.1 Mean number of abnormalities per subject of the normal control group and the pre-surgical patient subgroups (BB=bilateral)

	Mean			Standard deviation (S.D.)		
Normal control group	0.13			0.34		
Right hippocampal sclerosis	5.84			4.54		
Left hippocampal sclerosis	8.84			7.66		
	Right	Left	BB	Right	Left	BB

Non-hippocampal sclerosis	3.0	5.56	2.86	2.52	2.94	2.27
Normal MRI subgroup	4.47			3.66		

An Univariate ANOVA comparing the number of abnormal components per subject in the normal control group and the several patient subgroups showed a significant difference ($F(6,172) = 10.6$, $p=0.0001$). The application of Post-Hoc tests (Bonferroni) showed a significant larger number of abnormalities in the patient subgroups with left and right hippocampal sclerosis as compared with the normal control group. The comparison between the normal control group and the patients with non-hippocampal sclerosis lesions or normal MRI was not significant.

In order to compare amplitude and latency of the responses in each patient subgroup with the normal control group, a Multivariate Analysis of Variance was performed with contrasts followed by the Bonferroni correction. Due to their non-Gaussian distribution, amplitude and latency values were transformed into logarithms. The comparison of each subgroup with the other subgroups of patients was not significant for any waveform. The comparison between the patient subgroups and the normal control group was not significant for Onset amplitude, Frequency Change amplitude and latency and Mismatch amplitude. The comparison of the four subgroups of patients with the normal control group for the four waves (N1 right, P2 right, N1 left and P2 left) was significant for Onset latency ($F=2.56$ $(16,620)$, $p=0.001$) and Mismatch latency ($F= 2.32$, $(16,696)$, $p=0.002$):

-for Onset latency, the application of contrasts and the Bonferroni correction showed a significant difference for ON1 right (between the normal control group and right hippocampal sclerosis and normal MRI subgroups), for OP2 right (between the normal control group, the right and left hippocampal sclerosis and the normal MRI subgroups), for ON1 left (between the normal control group and the right and left hippocampal sclerosis subgroups) and for OP2 left (between the normal control group and right and left hippocampal sclerosis subgroup and normal MRI subgroups) . In summary, Onset latency for at least one component was significantly longer in three out of six patient subgroups when compared with the normal control group.

-for Mismatch latency, the application of contrasts and the Bonferroni correction showed a significant difference for MN1 right and MN1 left (between the normal control group and the left hippocampal sclerosis subgroup), for MP2 right (between the normal control group and all the patient subgroups) and MP2 left (between the normal control

group and the right and left hippocampal sclerosis subgroups). In summary, Mismatch latency for at least one component was significantly longer in all the patient subgroups when compared with the normal control group.

Paired T-tests were used to compare latency and amplitude values between right and left electrodes for each condition in each patient subgroup. They showed no significant inter-hemispheric latency differences or amplitude asymmetries that could be related to the underlying pathology in each subgroup of patients ($p<0.005$).

3.2.2 Patients with right hippocampal sclerosis (n=43)

N1 and P2 were present in all patients from this subgroup. The T-complex was considered to be present at electrode T4 in 38 subjects and at electrode T3 in 41 subjects for Onset, and in 37 (T4) and 35 (T3) subjects for Frequency Change. Figures 3.8, 3.9 and 3.10 show the waveforms obtained from patient A1, a right-handed, 31-year-old man with right hippocampal sclerosis and uncontrolled seizures for 25 years.

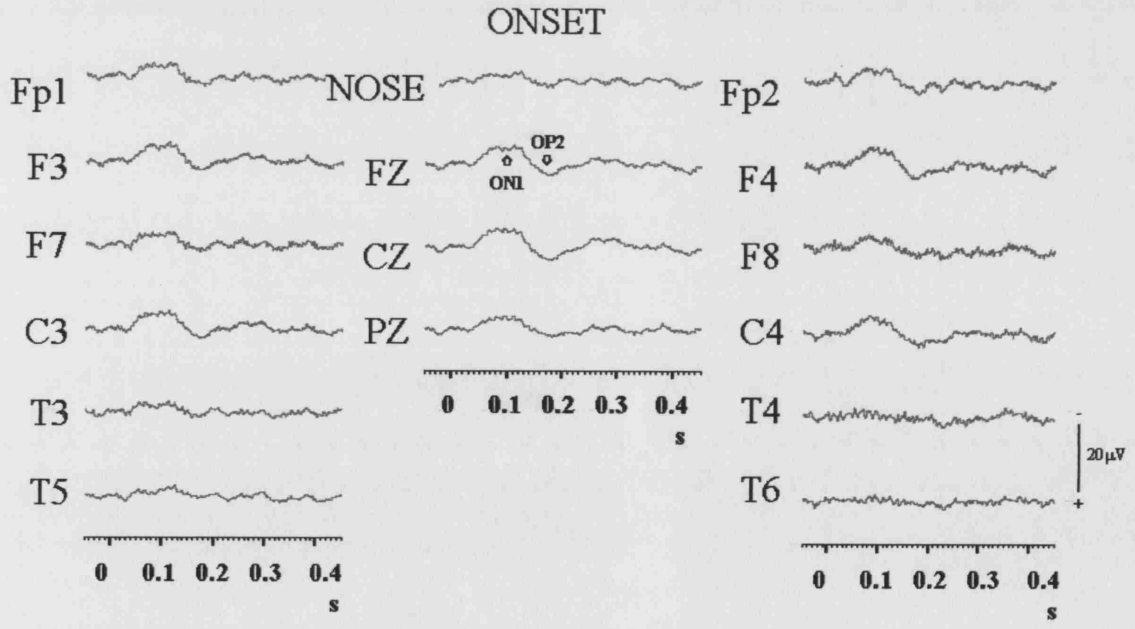

Fig. 3.8 Onset responses from patient A1. OP2 is of lower amplitude at left electrodes when compared with the limits obtained from the control group.

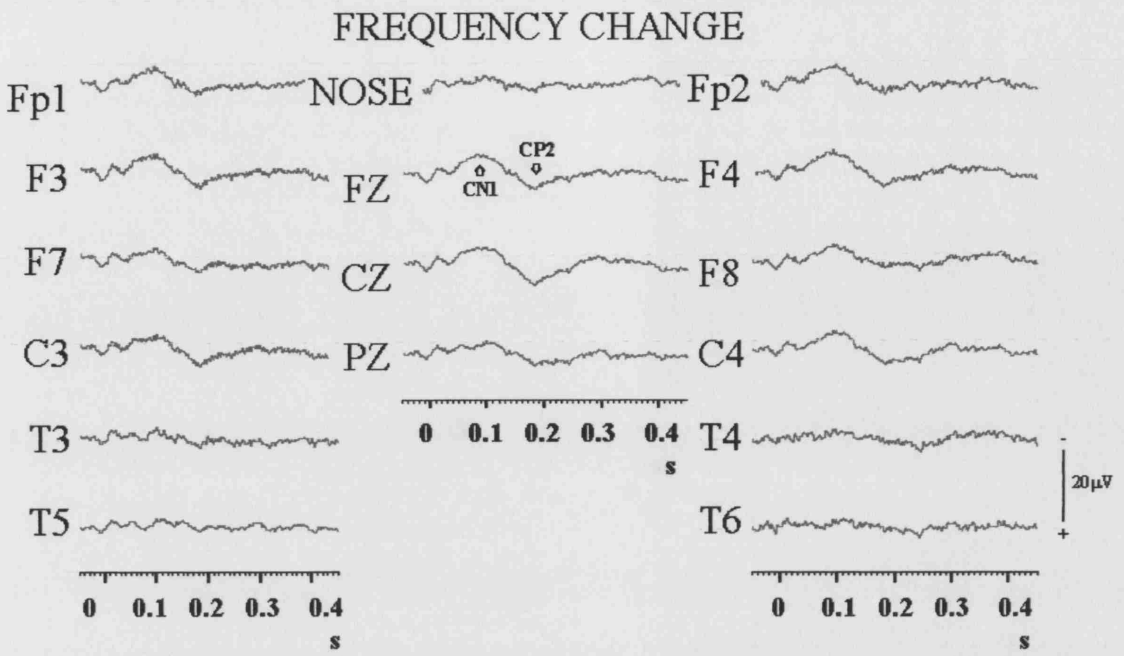

Fig. 3.9 Frequency Change responses from patient A1. No abnormalities were present for any component when compared with the limits obtained from the control group

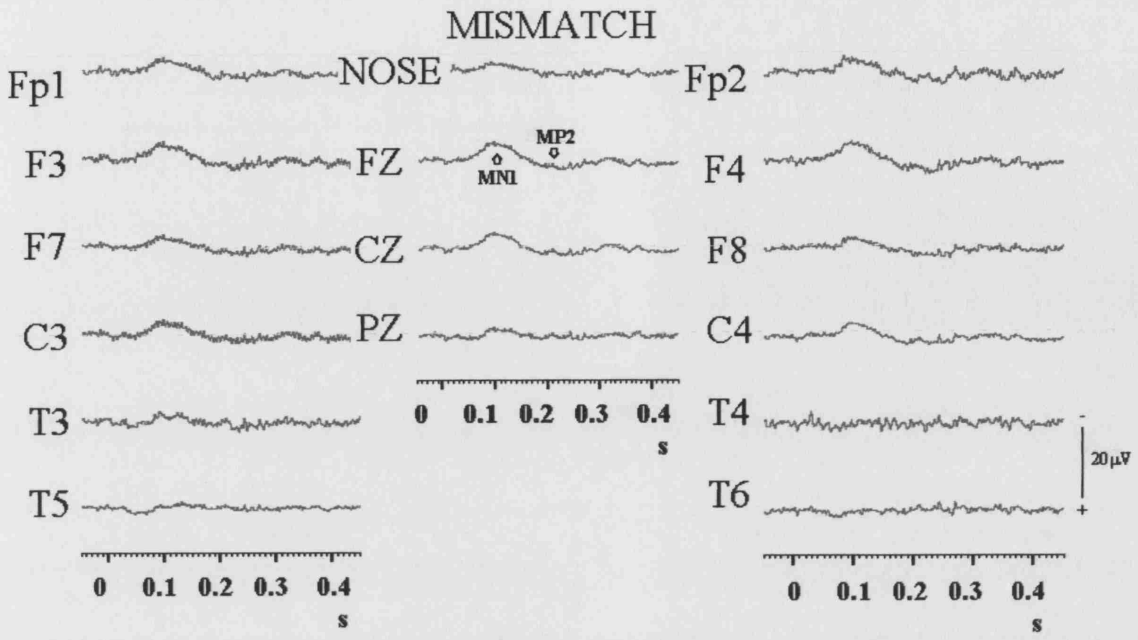

Fig. 3.10 Mismatch responses from patient A1. No abnormalities were present in any components when compared with the limits obtained from the control group

Figures 3.11, 3.12 and 3.13 show the group mean responses to Onset, Frequency Change and Mismatch from the right hippocampal sclerosis patients, superimposed on the group mean responses from the normal control group that are presented in black.

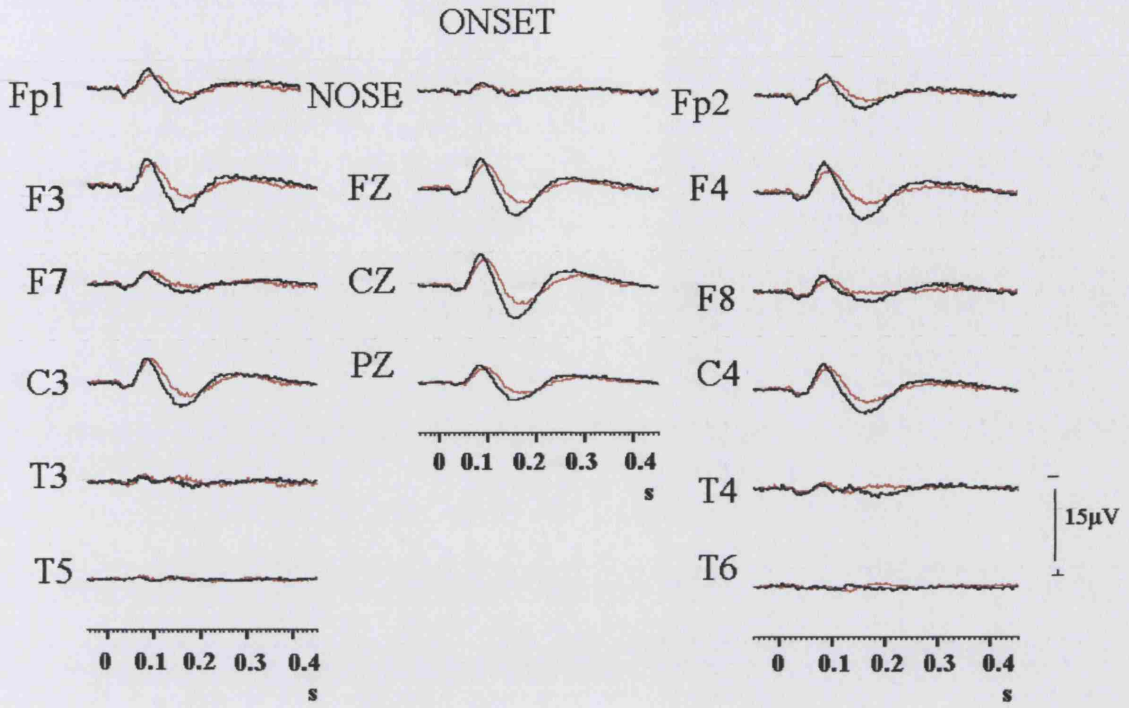

Fig. 3.11 Comparison of the average Onset responses from the normal control group and right hippocampal sclerosis subgroup. ON1 and OP2 were significantly delayed at right and left electrodes in the patient subgroup when compared with the control group. Control group is seen in black, patient subgroup is seen in red.

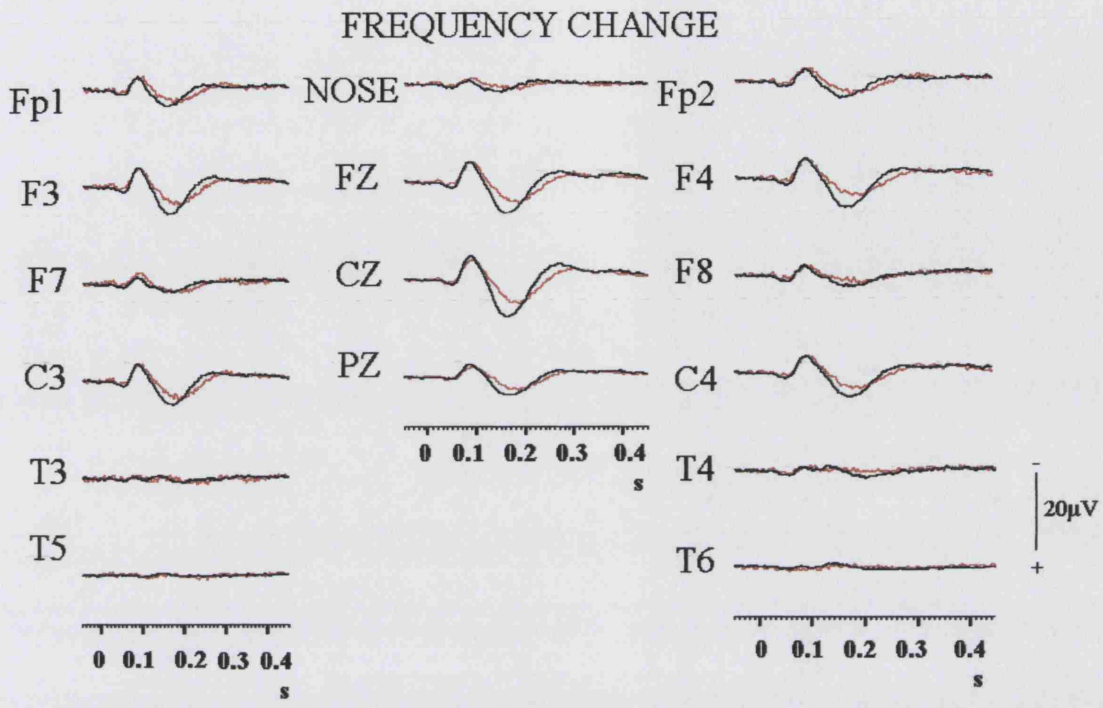

Fig. 3.12 Comparison of the average Frequency Change responses from the normal control group and the right hippocampal sclerosis subgroup. No significant differences were seen. Control group is seen in black, patient subgroup is seen in red.

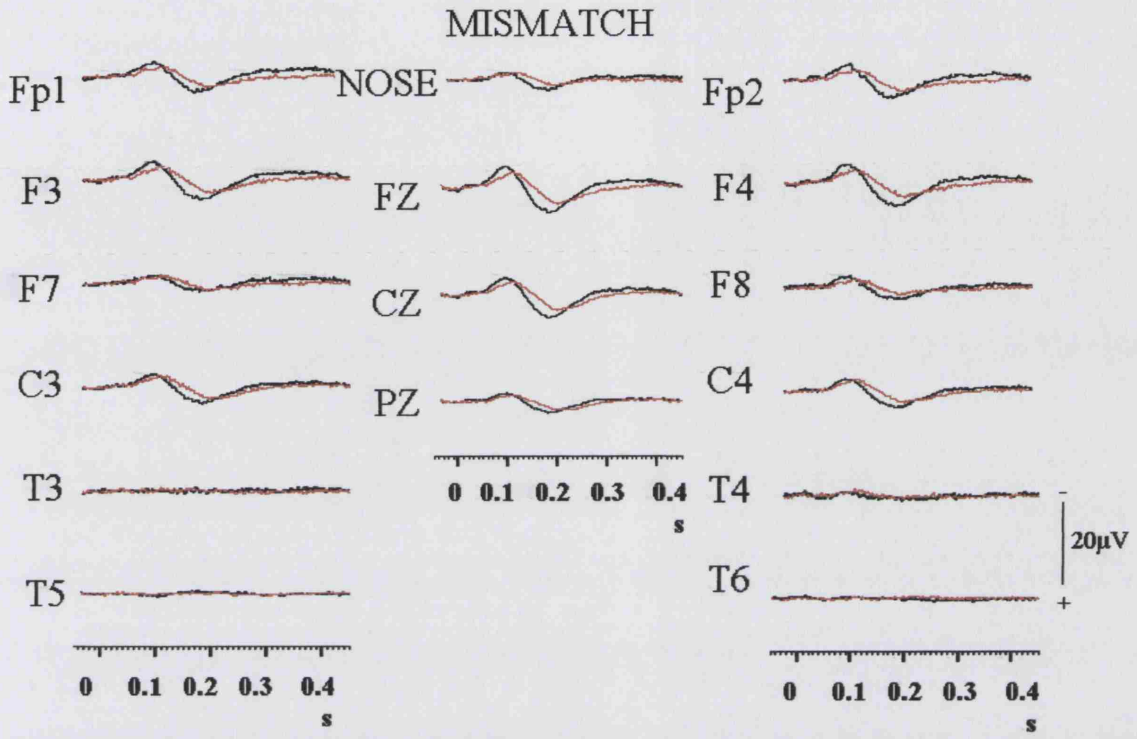

Fig. 3.13 Comparison of the average Mismatch responses from the normal control group and the right hippocampal sclerosis subgroup. No significant differences were seen for the MN1. The MP2 at right and left electrodes was significantly delayed in the patient subgroup when compared with the normal control group. Control group is seen in black, patient subgroup is seen in red.

The incidence of amplitude and latency abnormalities for the three stimuli in the right hippocampal sclerosis subgroup are summarised in table 3.2.

Table 3.2: Number of abnormal latency and amplitude values in the right hippocampal sclerosis subgroup (R= right. L= left, LAT= latency, AMP= amplitude)

LATENCY	**ONSET**		**FREQUENCY CHANGE**		**MISMATCH**	
	LAT	AMP	LAT	AMP	LAT	AMP
N1 R (F4, C4)	15 (35%)	0	4 (9%)	3 (7%)	4 (9%)	2 (5%)
P2 R (F4, C4)	15 (35%)	12 (28%)	15 (35%)	7 (16%)	12 (28%)	10 (23%)

N1 L (F3, C3)		14 (33%)	2 (5%)	7 (16%)	1 (2%)	7 (16%)	1 (2%)
P2 L (F3, C3)		24 (56%)	12 (28%)	17 (40%)	7 (16%)	12 (28%)	12 (28%)
N1 R-L	**Ratio N1**	9 (7 +, 2-)	1 (-)	6 (5+,1-)	4 (-)	4 (3 +, 1-)	6 (2 +, 4 -)
P2 R-L	**Ratio P2**	6 (1 +, 5-)	11 (5+,6-)	7 (2 +, 5 -)	6 (2 +,4 -)	6 (3 +, 3 -)	12 (7+,5 -)
T-complex (T4,T6)		----------	--------	16 (absent)	6 (T4)	--------	----------

χ^2 tests were performed to compare the incidence of positive and negative amplitude ratio and latency difference values between the patient subgroups and the group of normal controls in order to evaluate any lateralized abnormality produced by the subjacent pathology, but were not significant ($p<0.005$). Overall results are summarised in table 3.3:

Table 3.3: Summary of findings in the right hippocampal sclerosis subgroup.

Right hippocampal sclerosis subgroup abnormalities	**No. of abnormal subjects**	**%**
Overall incidence of abnormalities	41/43	95.4%
Right-sided abnormalities	35/43	81.4%
Left-sided abnormalities	37/43	86.1%
Onset response abnormalities	36/43	83.7%
Frequency Change response abnormalities	31/43	72.1%
Mismatch response abnormalities	29/43	67.4%
N1 abnormalities	23/43	53.5%
P2 abnormalities	38/43	88.4%
Latency abnormalities	37/43	86.0%
Amplitude abnormalities	30/43	69.8%
----------	----------	----------
Mean number of abnormalities per patient (x/13)	5.84	(S.D.=4.54)

Figure 3.14 presents a scatter graph for each waveform, comparing the pre-surgical values of the right hippocampal sclerosis subgroup with the normal limits obtained from the normal control group. The dark area represents the normal area for each component.

Right hippocampal sclerosis subgroup

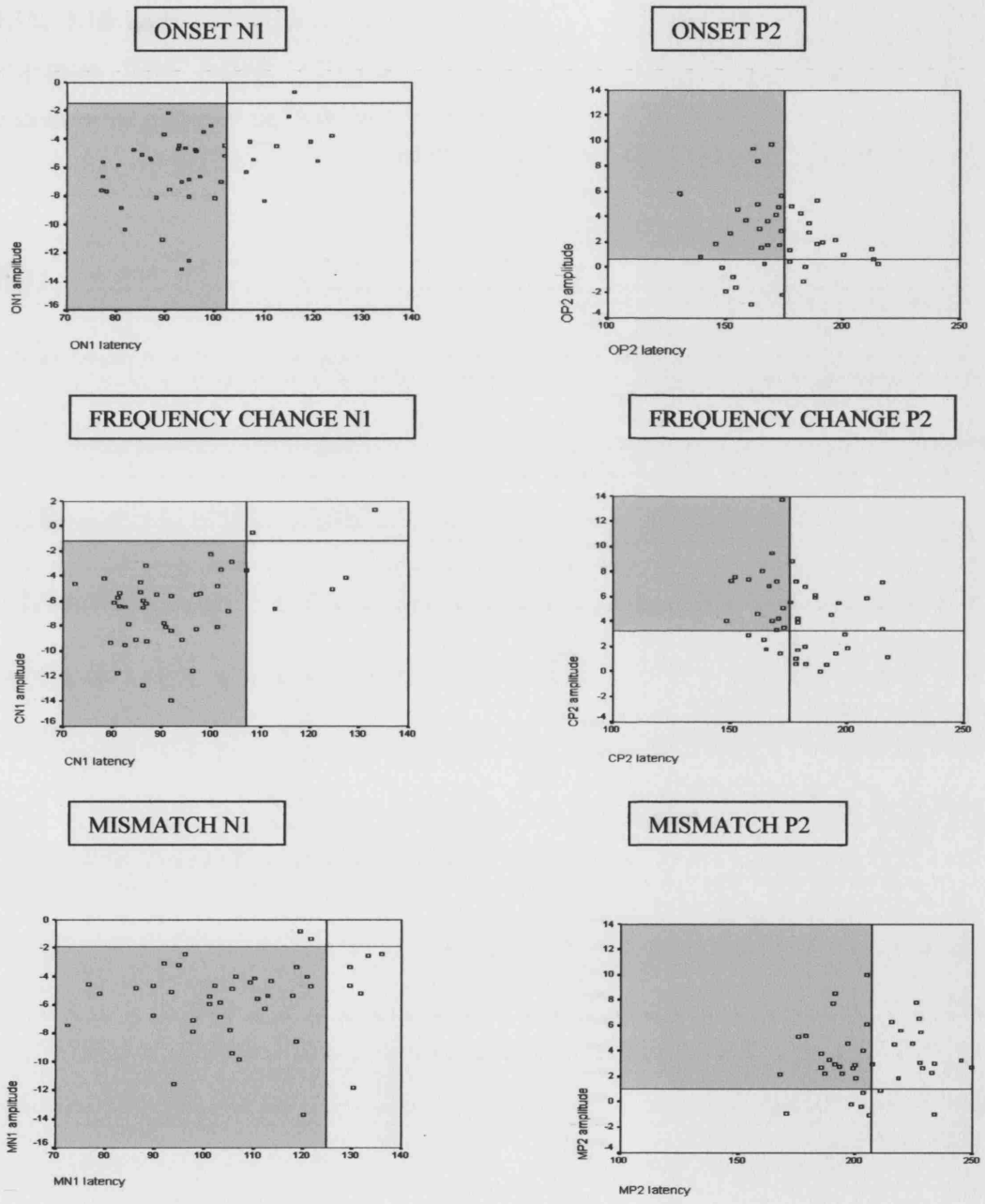

Fig.3.14 Scatter graphs from the different waveforms of the right hippocampal sclerosis subgroup, showing normal components in the dark area

3.2.3 Patients with left hippocampal sclerosis (n= 55)

The left hippocampal sclerosis subgroup was composed of 55 patients. N1 and P2 were present in all recordings. The T-complex was considered to be present in 46 (T4) and 37 (T3) patients to Onset and in 51(T4) and 48 (T3) patients to Frequency Change. Figure 3.15, 3.16 and 3.17 present respectively the Onset, Frequency Change and Mismatch responses from patient A33, a right-handed, 36-year-old woman with 33 years of uncontrolled epilepsy and left hippocampal sclerosis.

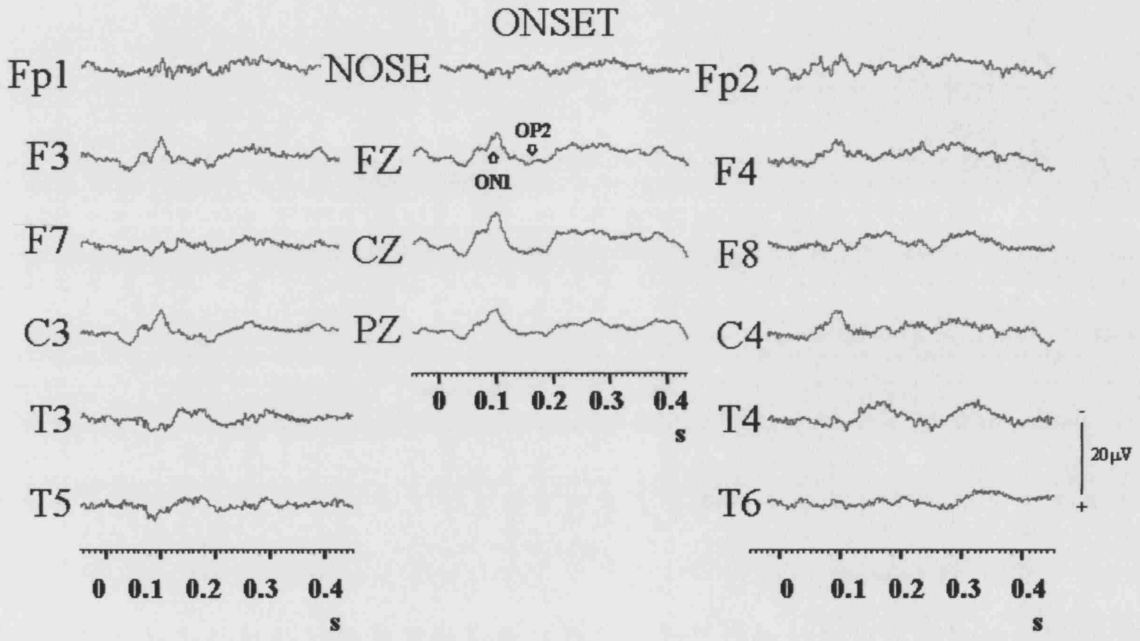

Fig. 3.15 Onset responses from patient A33. OP2 is abnormally delayed at both right and left electrodes when compared with the limits obtained from the control group.

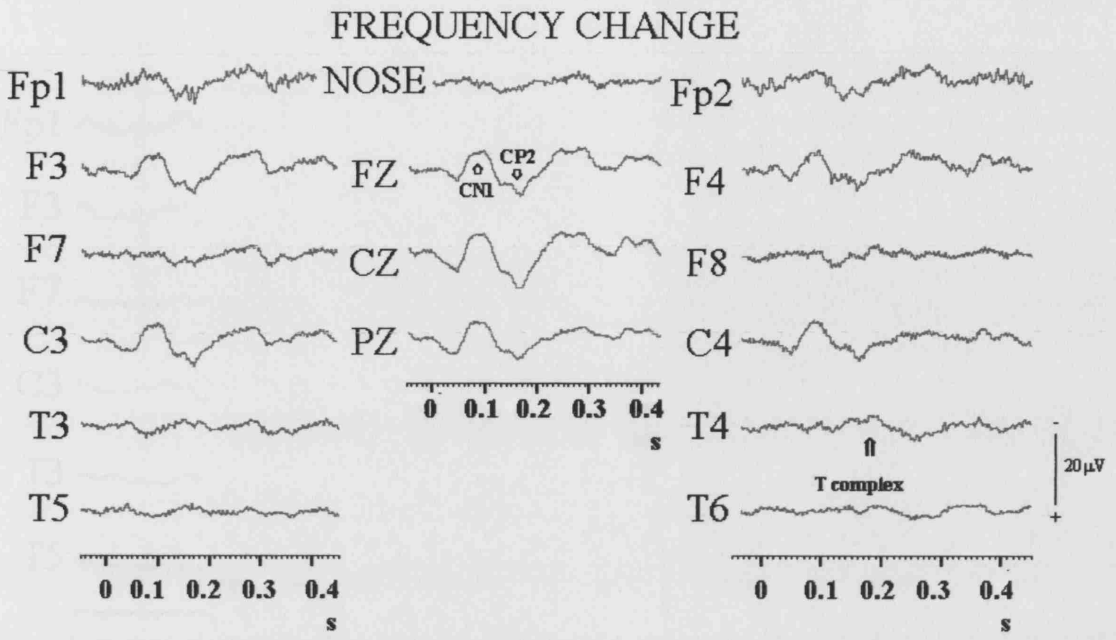

Fig.3.16 Frequency Change responses from patient A33. No abnormalities were seen for any of the components when compared with the limits obtained from the control group.

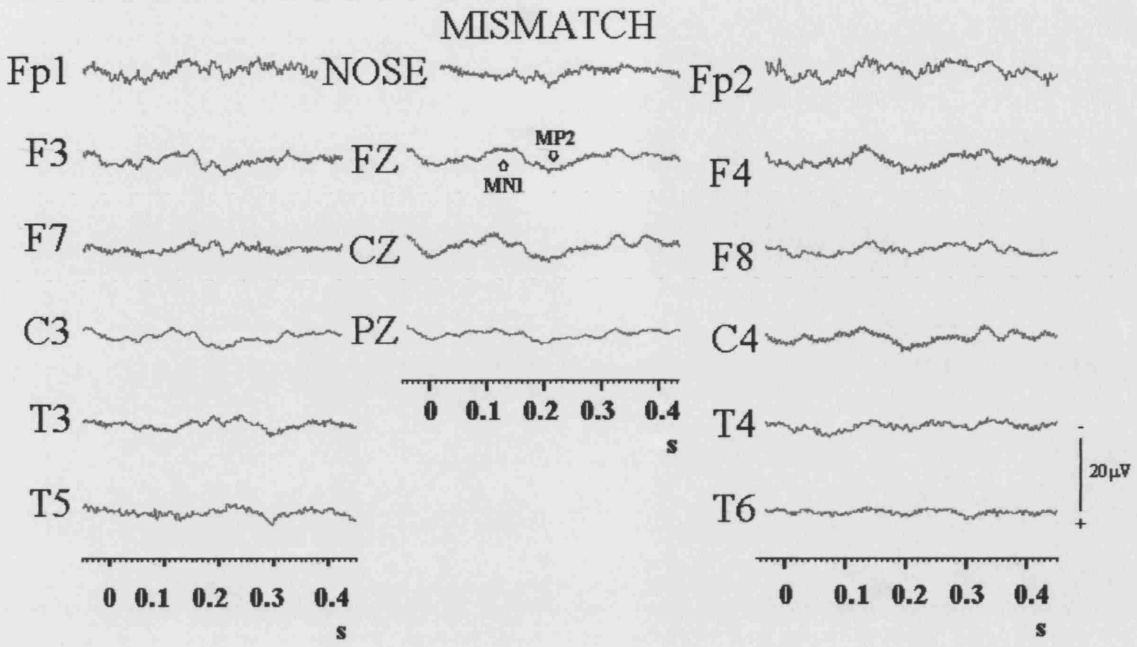

Fig. 3.17 Mismatch responses from patient A33. MN1 is delayed at right electrodes and MP2 is low in amplitude also at the right electrodes when compared with the limits obtained from the control group.

Figures 3.18, 3.19 and 3.20 show the group mean responses to Onset, Frequency Change and Mismatch from the left hippocampal sclerosis patients, superimposed on the group mean responses from the normal control group.

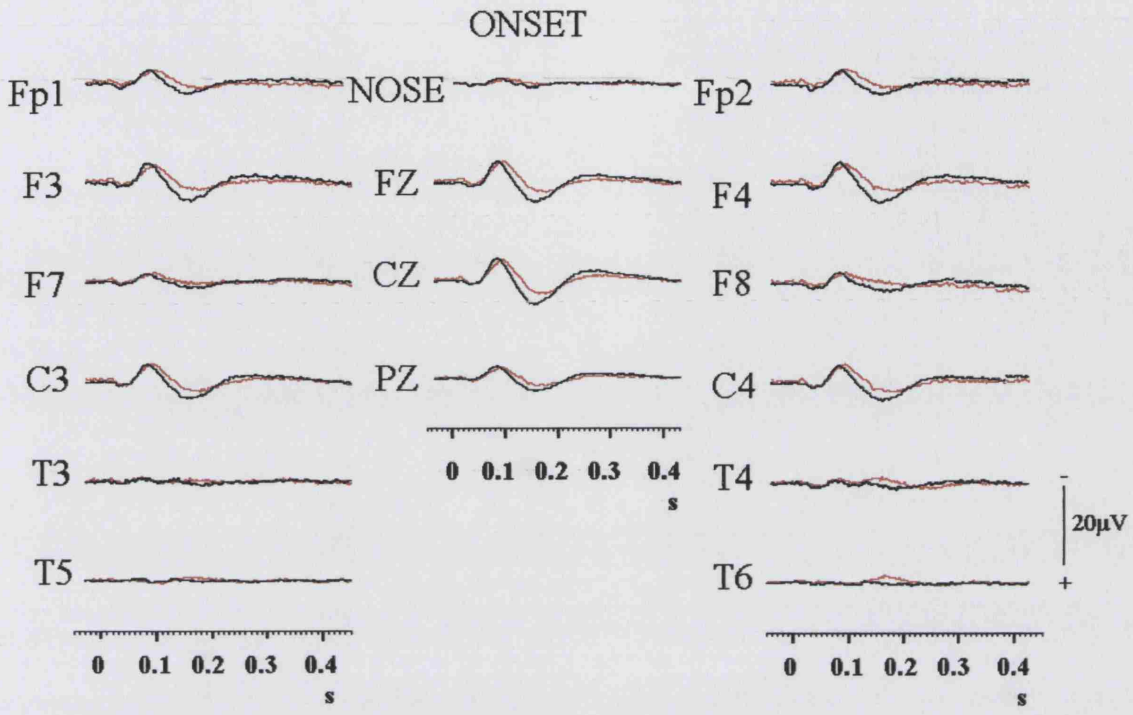

Fig. 3.18 Comparison of the average Onset responses from the normal control group and the left hippocampal sclerosis subgroup. OP2 at the right electrodes and ON1 and OP2 at the left electrodes were delayed in the patient subgroup when compared with the control group. Control group is seen in black, patient subgroup is seen in red.

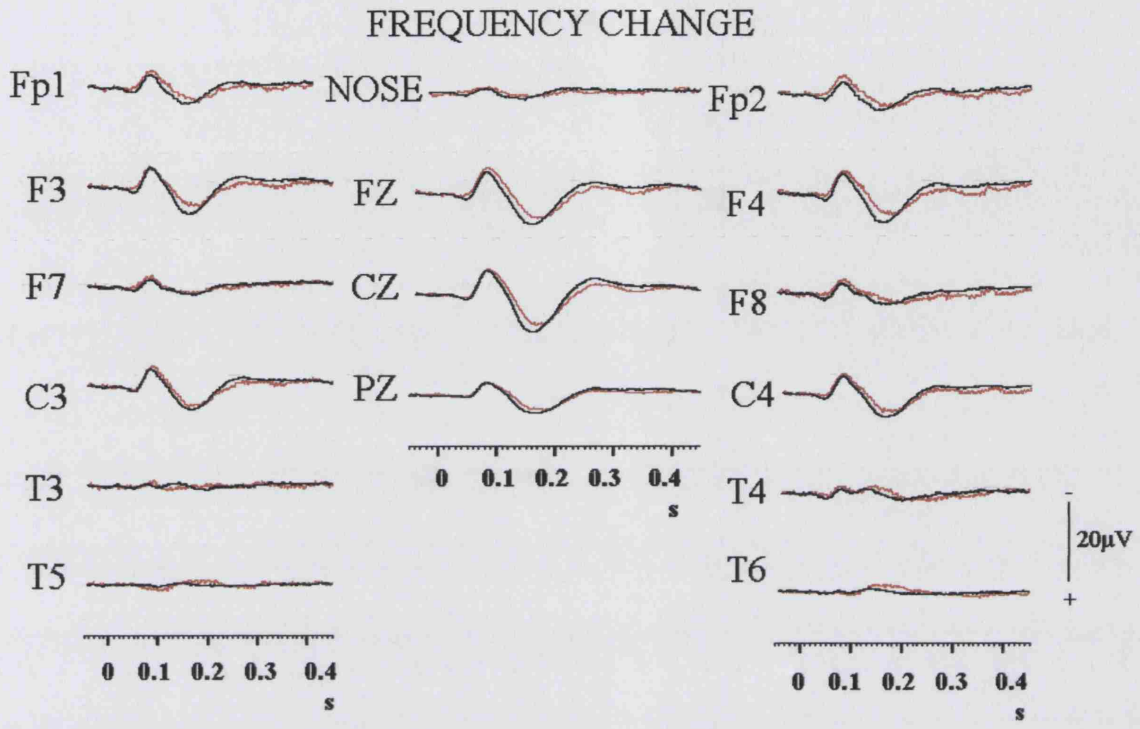

Fig. 3.19 Comparison of the average Frequency Change responses from the normal control group and the left hippocampal sclerosis subgroup. No significant differences were seen between the two groups. Control group is seen in black, patient subgroup is seen in red.

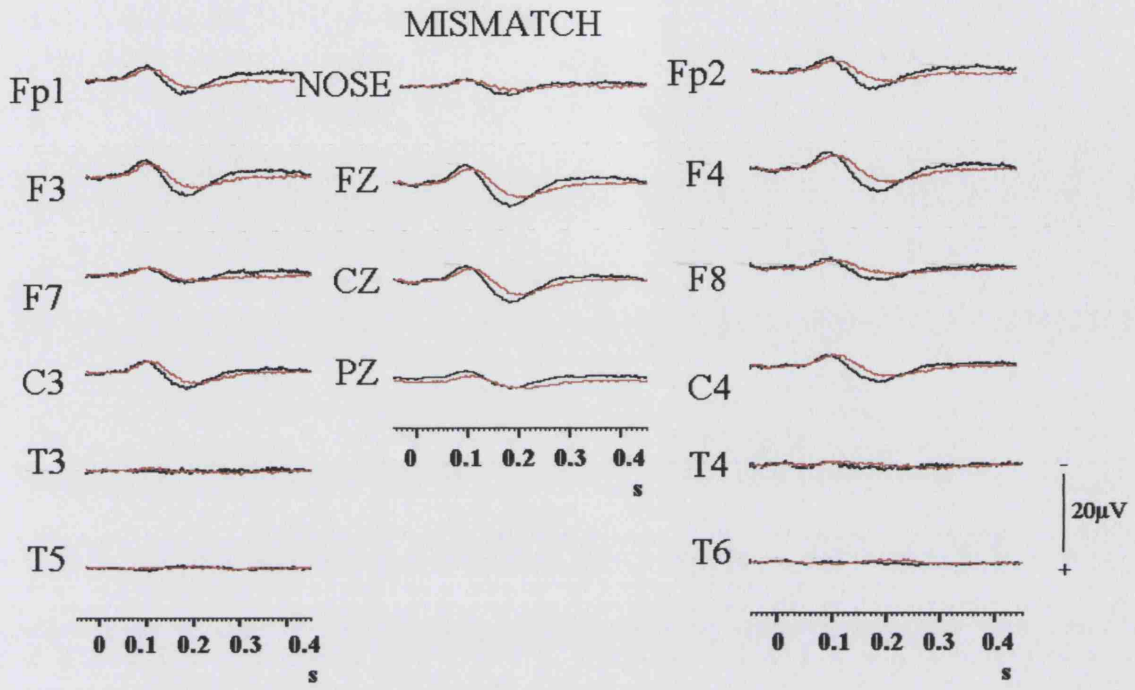

Fig. 3.20 Comparison of the average Mismatch responses from the normal control group and the left hippocampal sclerosis subgroup. MP2 was delayed at right and left electrodes in the patient subgroup when compared with the normal control group. Control group is seen in black, patient subgroup is seen in red.

Latency and amplitude values for each component were compared with the normal limits from the control group. The findings are summarised in table 3.4:

Table 3.4: Number of abnormal latency and amplitude values in the left hippocampal sclerosis subgroup (R= right. L= left, LAT= latency, AMP= amplitude)

LATENCY	**ONSET**		**FREQUENCY CHANGE**		**MISMATCH**	
	LAT	AMP	LAT	AMP	LAT	AMP
N1 R (F4, C4)	9 (16%)	2 (4%)	6 (11%)	3 (6%)	10 (18%)	2 (4%)
P2 R (F4, C4)	21 (38%)	12 (22%)	21 (38%)	9 (16%)	16 (29%)	13 (24%)

N1 L (F3, C3)		10 (18%)	1 (2%)	9 (16%)	4 (7%)	10 (18%)	4 (7%)
P2 L (F3, C3)		26 (47%)	15 (27%)	19 (35%)	5 (9%)	11 (20%)	9 (16%)
N1 R-L	**Ratio N1**	11 (6+,5-)	4 (2+,2-)	8 (3+,5-)	6 (2+,4-)	6 (3+,3-)	7 (4+,3-)
P2 R-L	**Ratio P2**	11 (5+,6-)	21 (15+,6-)	4 (1+,3-)	9 (3+,6-)	13 (8+,5-)	17 (9+,8-)
T-complex (T4,T6)		----------	----------	21 (absent)	4 (T4)	--------	--------

χ^2 tests were used comparing the incidence of positive and negative amplitude ratio and latency difference values between the normal control group and the left hippocampal sclerosis subgroup, but were not significant ($p<0.005$). The findings in the left hippocampal sclerosis group are summarised in table 3.5.

Table 3.5: Summary of main findings in left hippocampal sclerosis subgroup

Left hippocampal sclerosis subgroup abnormalities	**No. of abnormal subjects**	**%**
Overall incidence of abnormalities	54/55	98.2%
Right-sided abnormalities	48/55	87.3%
Left-sided abnormalities	44/55	80.0%
Onset response abnormalities	44/55	80.0%
Frequency Change response abnormalities	42/55	76.4%
Mismatch response abnormalities	44/55	80.0%
N1 abnormalities	27/55	49.0%
P2 abnormalities	47/55	85.5%
Latency abnormalities	49/55	89.1%
Amplitude abnormalities	38/55	69.1%
----------	----------	----------
Mean number of abnormalities per patient (x/13)	8.84	(S.D.=7.66)

χ^2 tests were used to compare the incidence of abnormalities between the right and left hippocampal sclerosis subgroups, but were not significant ($p<0.005$). Figure 3.21 presents a scatter graph for each waveform of the left hippocampus sclerosis subgroup, comparing the pre-surgical values of the left hippocampal sclerosis subgroup with the normal limits obtained from the normal control group. The dark area represents the normal area for each component.

Left hippocampal sclerosis subgroup

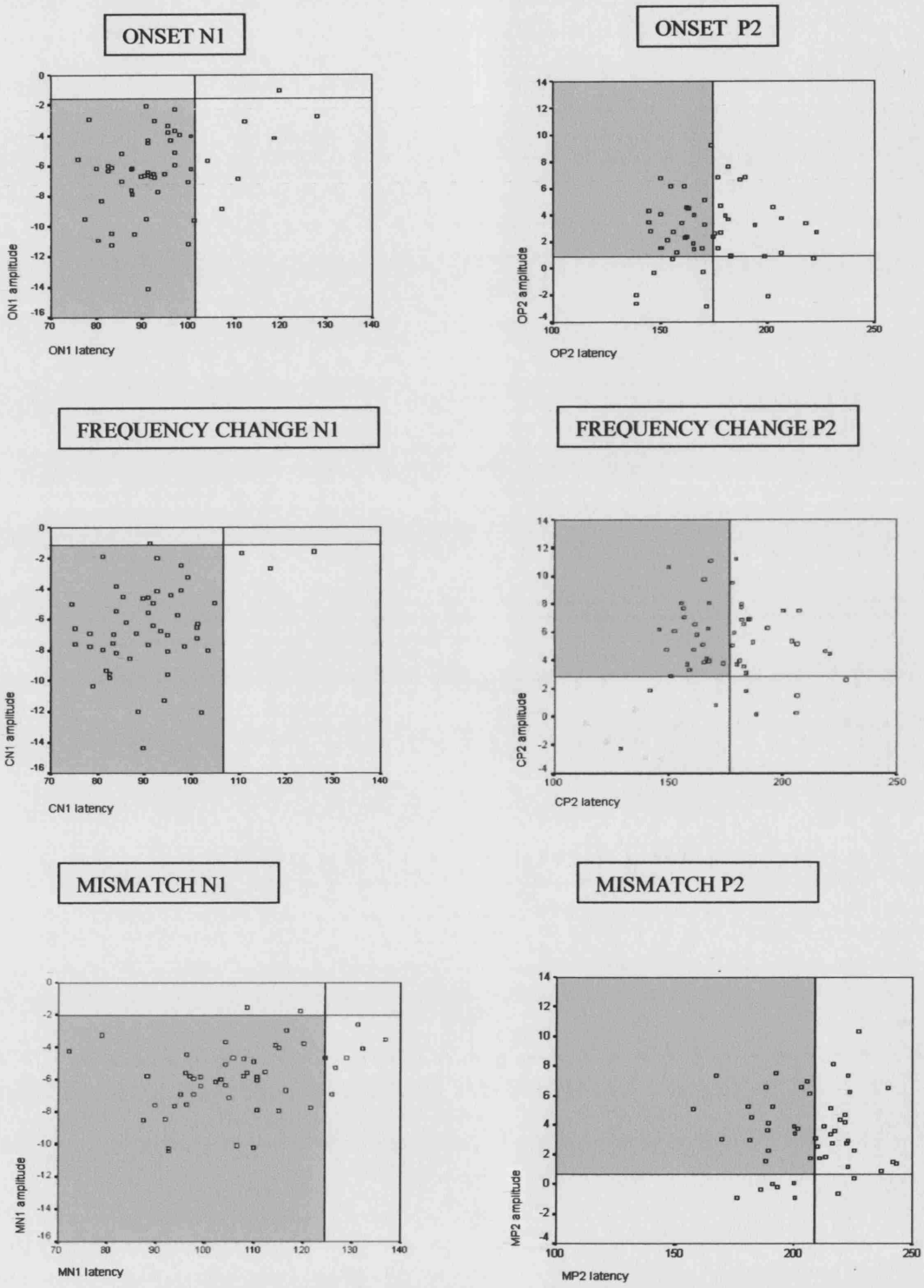

Fig.3.21 Scatter graphs from the different waveforms of the left hippocampal sclerosis subgroup, showing normal components in the dark area

3.2.3.1 Summary of the right and left hippocampal sclerosis subgroup results

No significant differences between the number and type of abnormalities as well as between mean amplitude and latency were seen between the right hippocampal sclerosis and left hippocampal sclerosis subgroups. Both subgroups presented a large percentage of abnormal subjects when compared with the normal group and the number of abnormalities per patient was significantly larger for the right hippocampal sclerosis and the left hippocampal sclerosis than for the normal control group, as seen before. There was no laterality effect over amplitude or latency in each subgroup, and the distribution of positive and negative values for amplitude ratios and latency differences were not significantly different from the normal control group.

Onset and Mismatch conditions showed significant increased latency responses for both subgroups, when compared with the normal control group, as seen before.

3.2.4 Patients with lesions that are not hippocampal sclerosis (n=35) or with normal MRI (n=15)

A similar analysis was performed of the incidence of abnormalities in the non-hippocampal sclerosis subgroup and in the subgroup of patients with normal MRI. The overall findings are summarised in tables 3.6 and 3.7

Table 3.6: Summary of main findings in the non-hippocampal sclerosis subgroup.

Number of abnormal subjects	Right-sided lesions	Left-sided lesions	Bilateral lesions
Overall incidence of abnormalities	11/12 (91.7%)	16/16 (100%)	7/7 (100.0%)
Right-sided abnormalities	10/12 (83.3%)	15/16 (93.8%)	7/7 (100.0%)
Left-sided abnormalities	8/12 (66.7%)	13/16 (81.3%)	5/7 (71.4%)
Onset response abnormalities	8/12 (66.7%)	15/16 (93.8%)	4/7 (55.1%)
Frequency Change response abnormalities	7/12 (58.3%)	13/16 (81.3%)	5/7 (71.4%)
Mismatch response abnormalities	8/12 (66.7%)	15/16 (93.8%)	4/7 (57.1%)

N1 abnormalities	5/12 (42.1%)	12/16 (75.0%)	2/7 (28.6%)
P2 abnormalities	10/12 (83.3%)	14/16 (87.5%)	7/7 (100.0%)
Latency abnormalities	10/12 (83.3%)	15/16 (93.8%)	6/7 (85.7%)
Amplitude abnormalities	6/12 (50.0%)	15/16 (93.8%)	7/7 (100.0%)
Mean number of abnormalities per patient (x/13)	3.0 (S.D.=2.52)	5.56 (S.D.=2.94)	2.86 (S.D.=2.27)

Table 3.7: Summary of main findings in the normal MRI subgroup

Normal MRI subgroup	**No. of abnormal subjects**	**%**
Overall incidence of abnormalities	15/15	100.0%
Right-sided abnormalities	15/15	100.0%
Left-sided abnormalities	12/15	80.0%
Onset response abnormalities	12/15	80.0%
Frequency Change response abnormalities	15/15	100.0%
Mismatch response abnormalities	10/15	66.7%
N1 abnormalities	11/15	73.3%
P2 abnormalities	15/15	100.0%
Latency abnormalities	15/15	100.0%
Amplitude abnormalities	12/15	80.0%
Mean number of abnormalities per patient (x/13)	4,47	(S.D.=3.66)

Figures 3.22, 3.23 and 3.24 show the group mean responses to Onset, Frequency Change and Mismatch from the non-hippocampal lesions subgroup of patients, superimposed on the group mean responses from the normal control group that is represented in black.

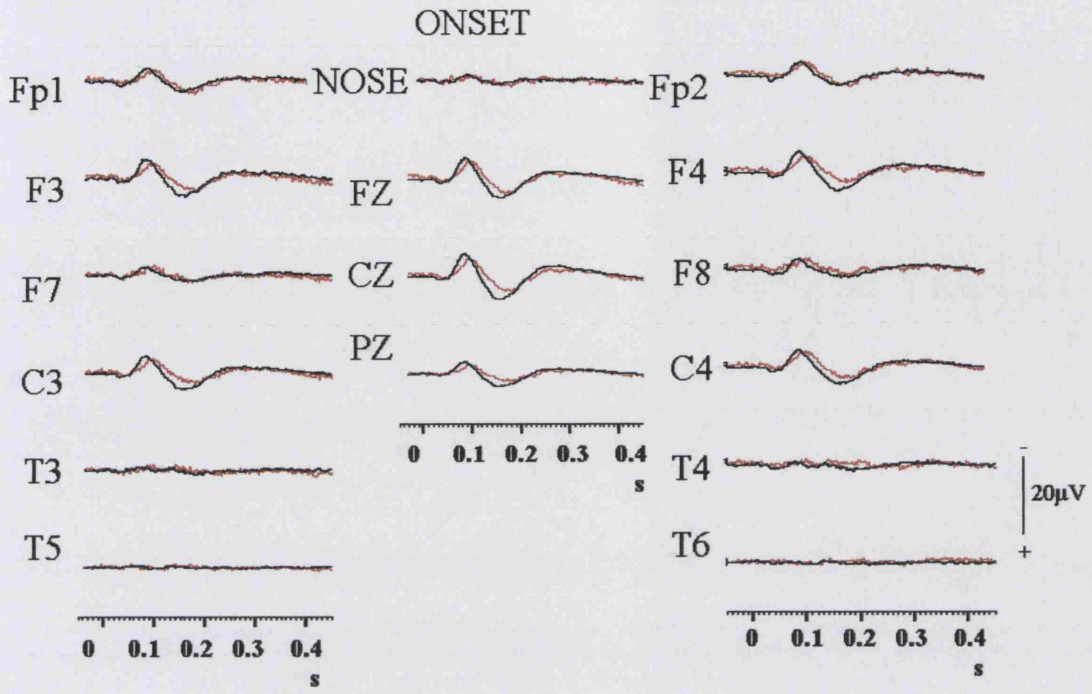

Fig. 3.22 Comparison of the Onset average responses from the normal control group and the right-sided lesions non-hippocampal sclerosis subgroup. No significant differences were seen for any component between the two groups. Control group is seen in black, patient subgroup is seen in red.

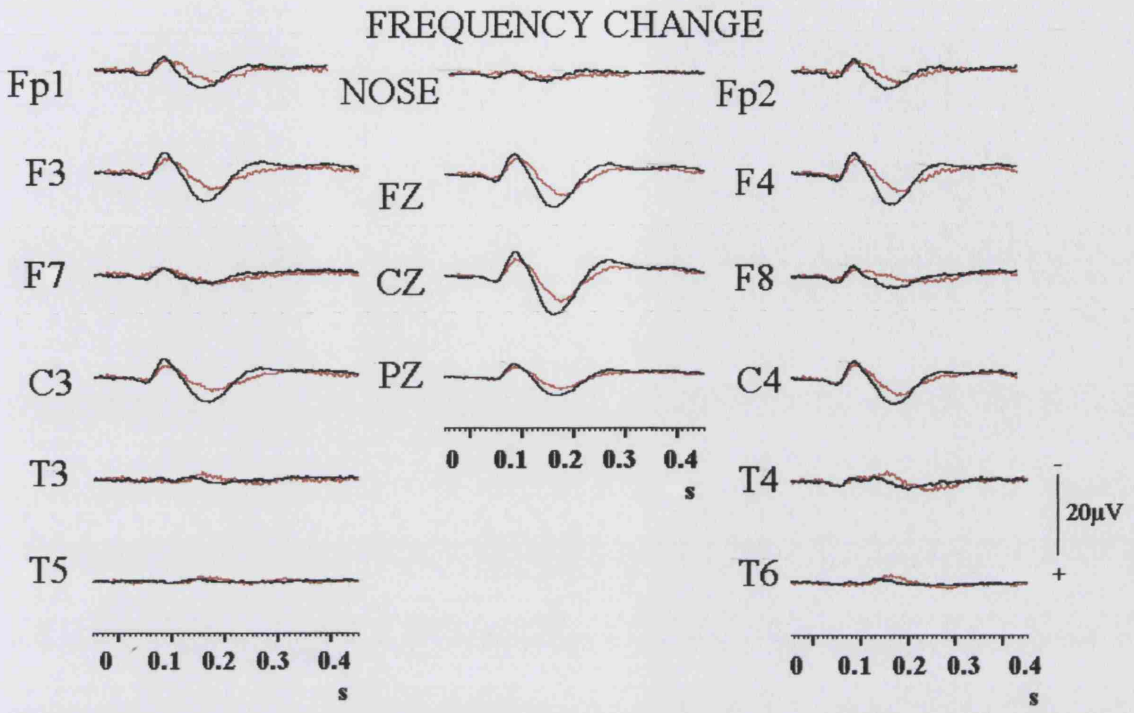

Fig. 3.23 Comparison of the Frequency Change average responses from the normal control group and the left-sided lesions non-hippocampal sclerosis subgroup. No significant differences were seen for any component between the two groups. Control group is seen in black, patient subgroup is seen in red.

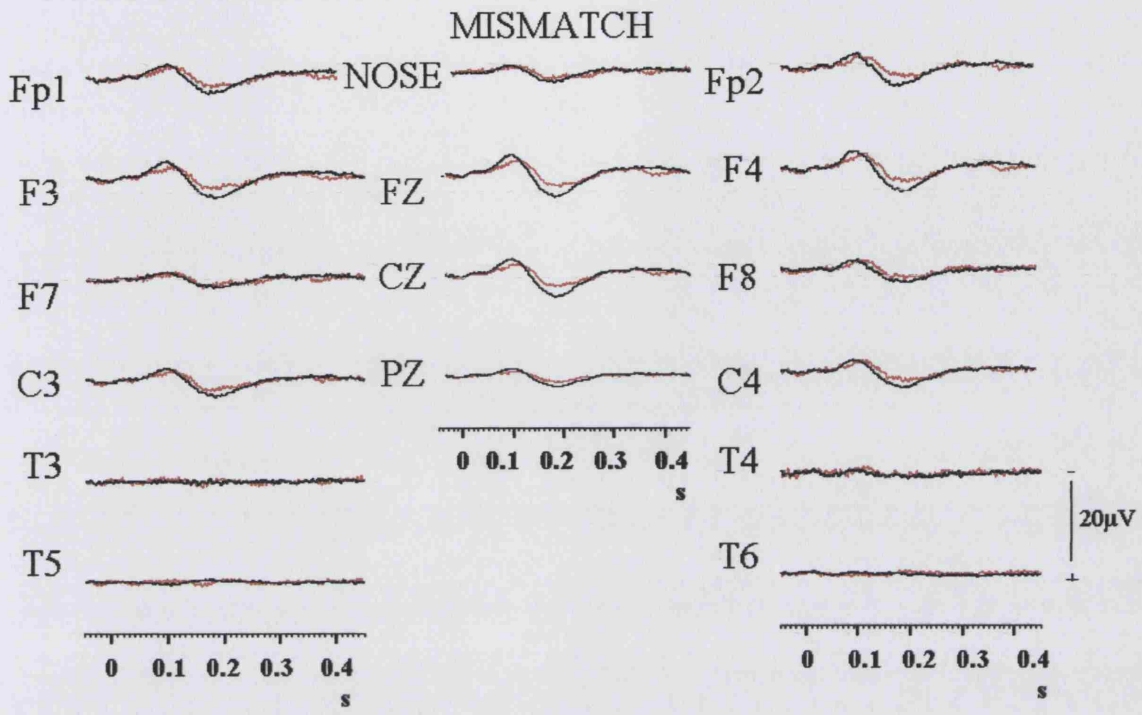

Fig. 3.24 Comparison of the Mismatch average responses from the normal control group and the bilateral lesions non hippocampal sclerosis subgroup. No significant differences were seen for any component between the two groups. Control group is seen in black, patient subgroup is seen in red.

Figure 3.25 presents a scatter graph for each waveform, comparing the pre-surgical values of the non-hippocampal sclerosis subgroup with the normal limits obtained from the normal control group. The dark area represents the normal area for each component.

Non-hippocampal sclerosis lesions subgroup

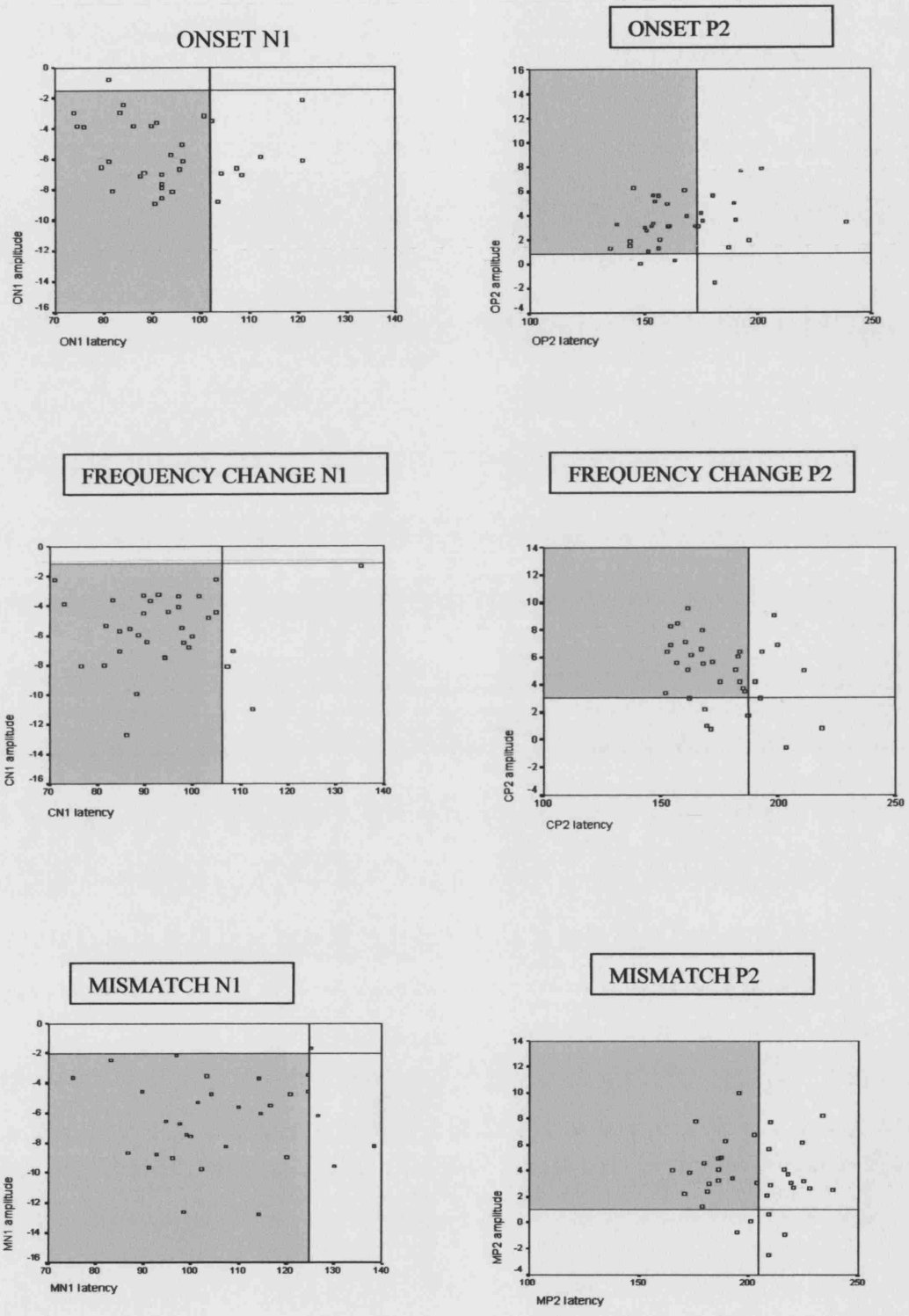

Fig. 3.25 Scatter graphs from the different waveforms of the non-hippocampal sclerosis subgroup, showing normal components in the dark area

Figure 3.26, 3.27 and 3.28 show the group mean responses to Onset, Frequency Change and Mismatch from the normal MRI subgroup of patients, superimposed on the group mean responses from the normal control group that is represented in black.

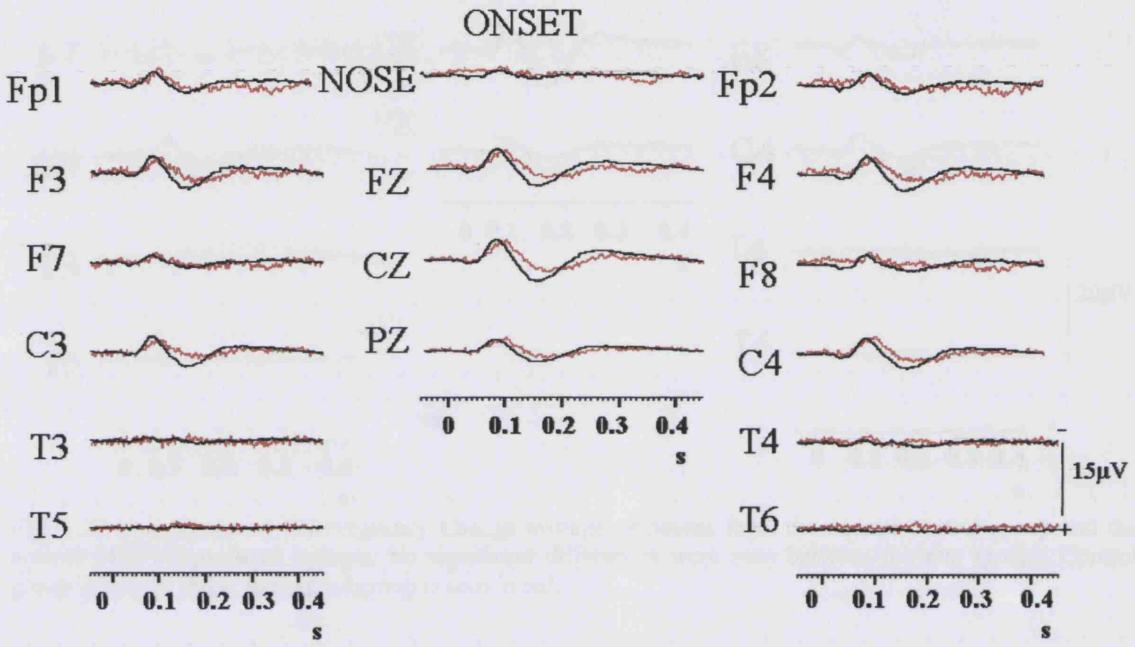

Fig. 3.26 Comparison of the Onset average responses from the normal control group and the normal MRI subgroup of patients. ON1 on the right and OP2 on the left hemisphere were significantly delayed when compared with the control group. Control group is seen in black, patient subgroup is seen in red.

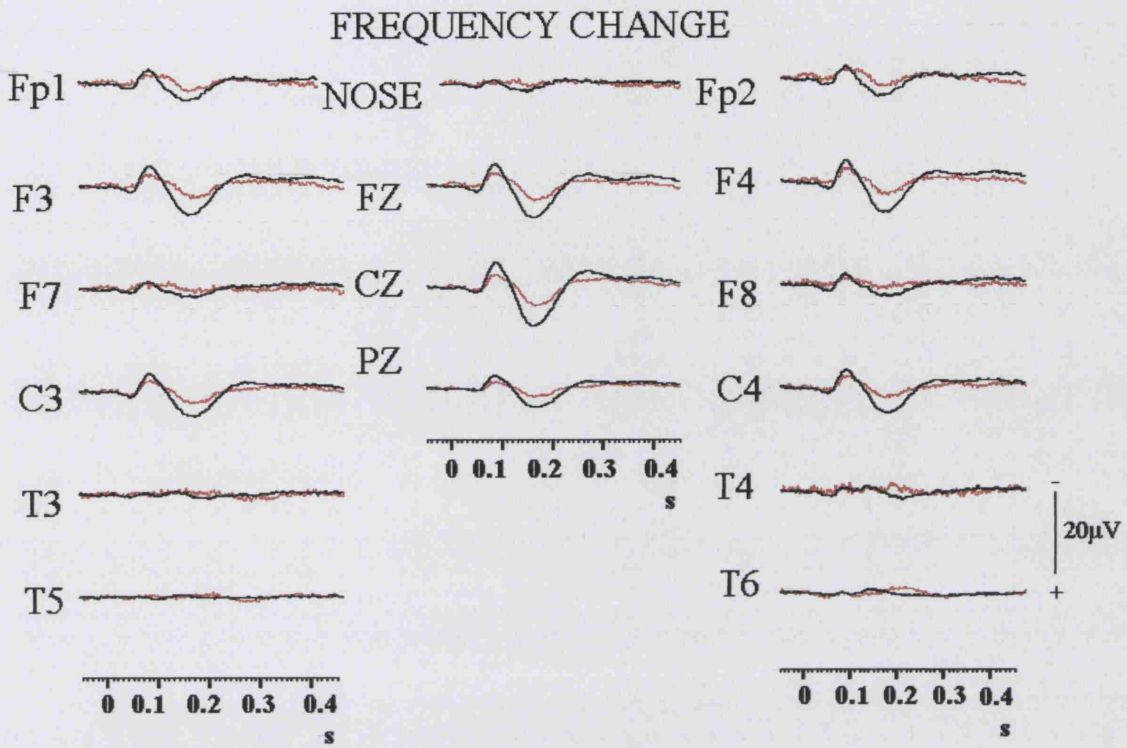

Fig. 3.27 Comparison of the Frequency Change average responses from the normal control group and the normal MRI subgroup of patients. No significant differences were seen between the two groups. Control group is seen in black, patient subgroup is seen in red.

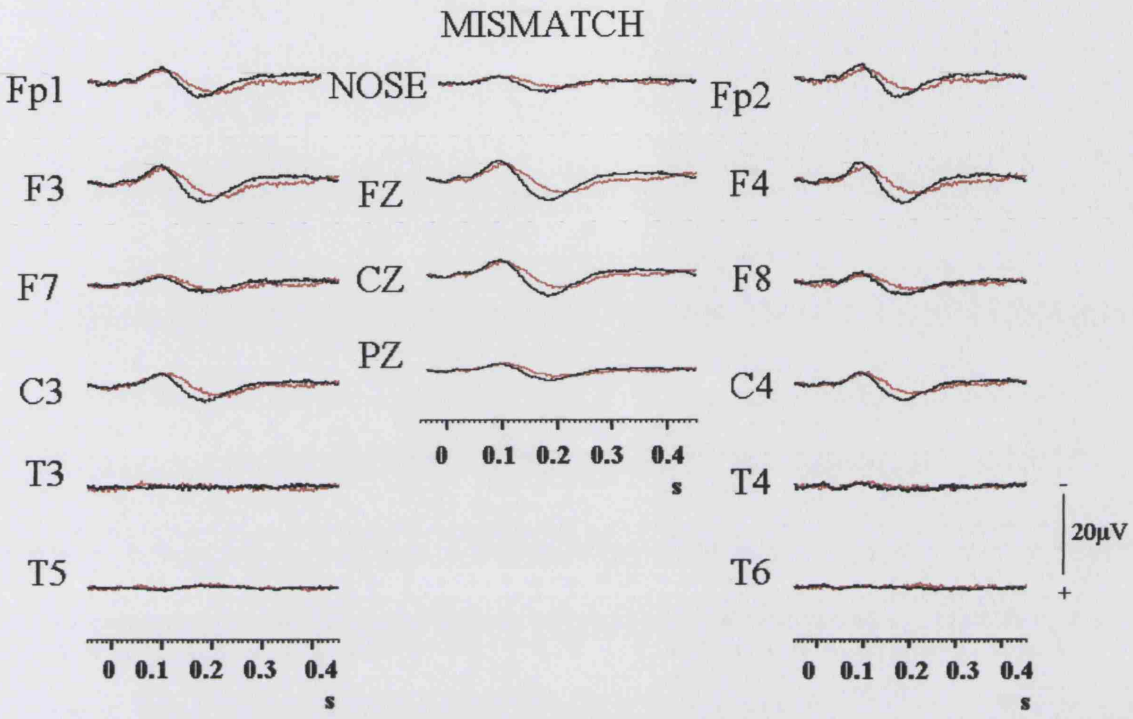

Fig. 3.28 Comparison of the Mismatch average responses from the normal control group and the normal MRI subgroup of patients. No significant differences were seen for MN1. MP2 at the right electrodes was significantly delayed in the patient subgroup when compared with the control group. Control group is seen in black, patient subgroup is seen in red.

Figure 3.29 presents a scatter graph for each waveform, comparing the pre-surgical values of the normal MRI subgroup with the normal limits obtained from the normal control group. The dark area represents the normal area for each component.

Normal MRI subgroup

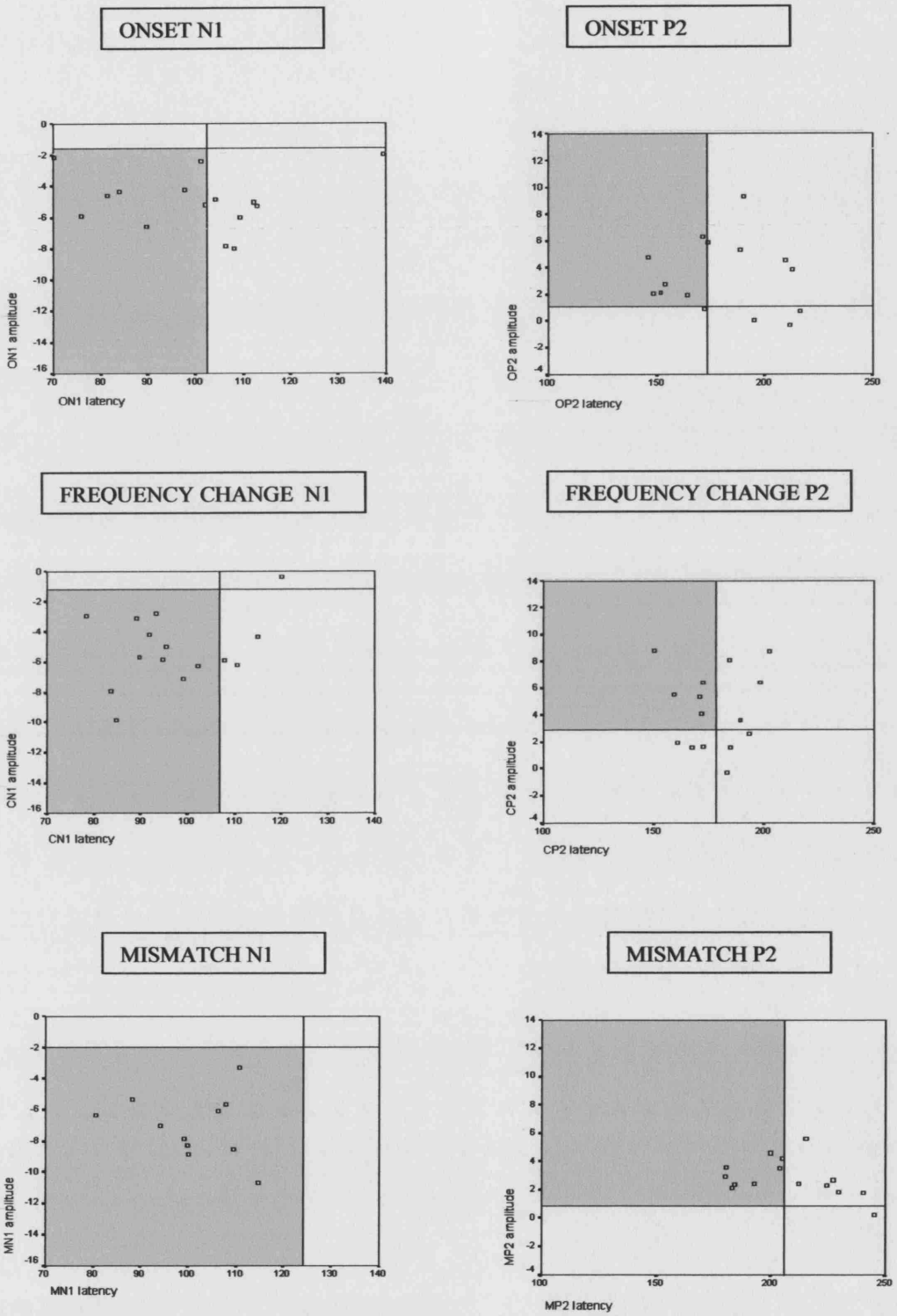

Fig. 3.29 Scatter graphs from the different waveforms of the normal MRI subgroup, showing normal components in the dark area

3.2.5 Conclusion of pre-surgical analysis

The findings of ANOVA indicate a significant delay for Onset and Mismatch responses in the patients with hippocampal sclerosis (right- or left-sided) and in the patients with normal MRI. Mismatch responses were significantly delayed in these subgroups and also in the non-hippocampal sclerosis subgroup of patients. Frequency Change responses were not significantly affected, nor was there any significant effect on the amplitudes of all three responses.

When the patients were considered in an individual basis the incidence of abnormal auditory evoked potentials (in terms of amplitude or latency) in each patient subgroup was very high (between 95.4 and 100%) and similar. Left and right-sided abnormalities were similarly frequent in all groups as were Onset, Frequency Change and Mismatch abnormalities. There was therefore no suggestion of any association between the hemisphere showing abnormal auditory evoked potentials and the side of hippocampal sclerosis or non-hippocampal sclerosis lesions. However, it is possible that the responses recorded at F3/F4 and C3/C4 did not arise exclusively in the underlying hemisphere.

There was no significant difference in the distribution of positive and negative values of the amplitude ratios and latency differences between the patient subgroups, also indicating no evidence of any lateralized effect of unilateral hippocampal sclerosis on the auditory evoked potentials.

Owing to the many comparisons performed, the presence of Type I error cannot be excluded in the inter-group comparison or the assessment of individual patients. However, as far as the latter is concerned, the incidence of "abnormal" auditory evoked potentials measures in the normal control group was much lower than in any of the patient subgroups (on average 0.13 abnormalities per normal subject, as compared with 2.86 to 8.84 for each of the patient subgroups).

3.3 Surgical evaluation

3.3.1 Normal control test/retest variability for surgical evaluation

To determine the degree of variability between serial recordings in the same way as with surgical patients, a subgroup of 15 normal subjects was recorded twice, with an interval of 6-12 months. Figures 3.26, 3.27 and 3.28 show average waveforms from a normal control subject.

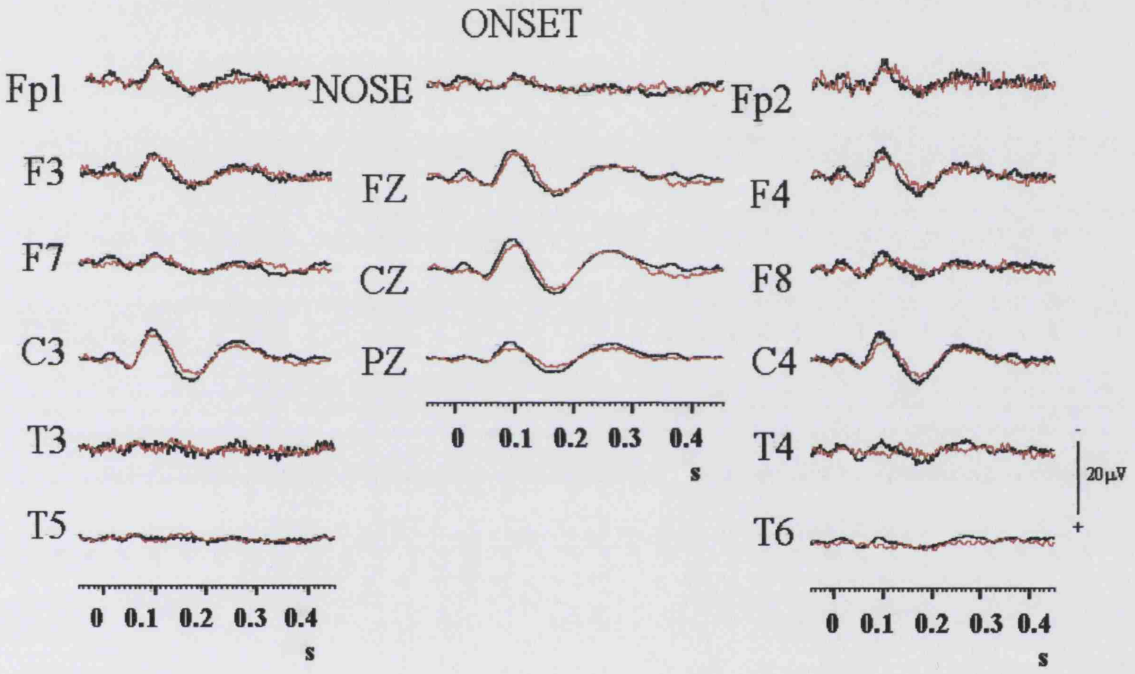

Fig. 3.26 Onset responses separated by 6 months from a normal control subject (n9). The second recording is represented in black.

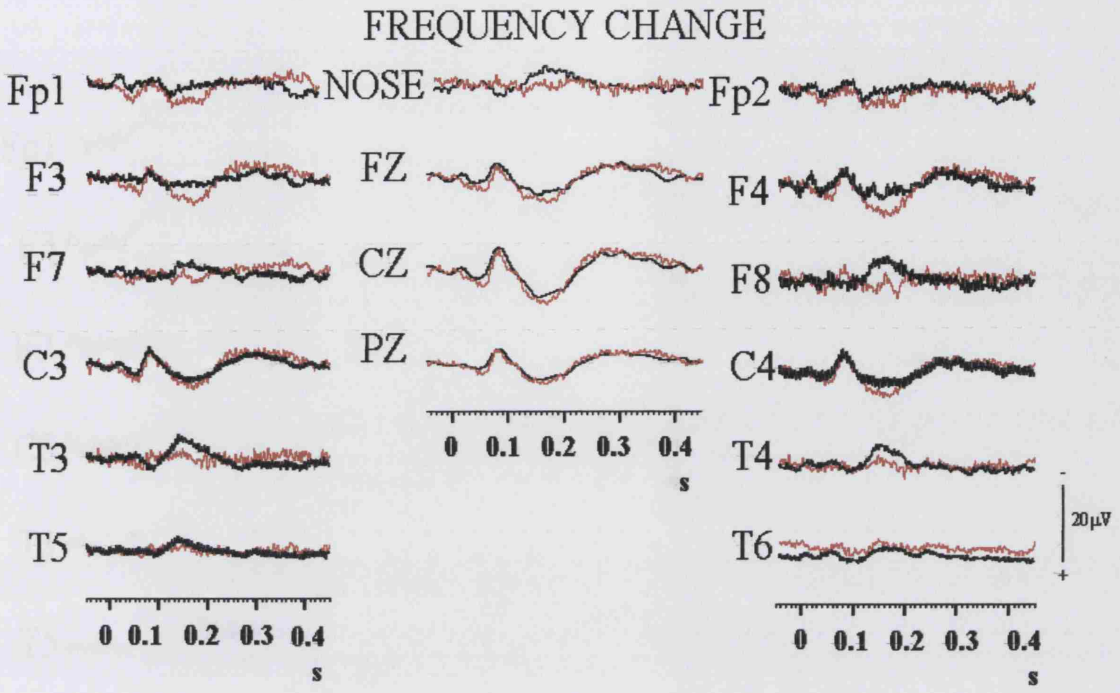

Fig. 3.27 Frequency Change responses separated by 6 months from a normal control subject (n9). The second recording is represented in black.

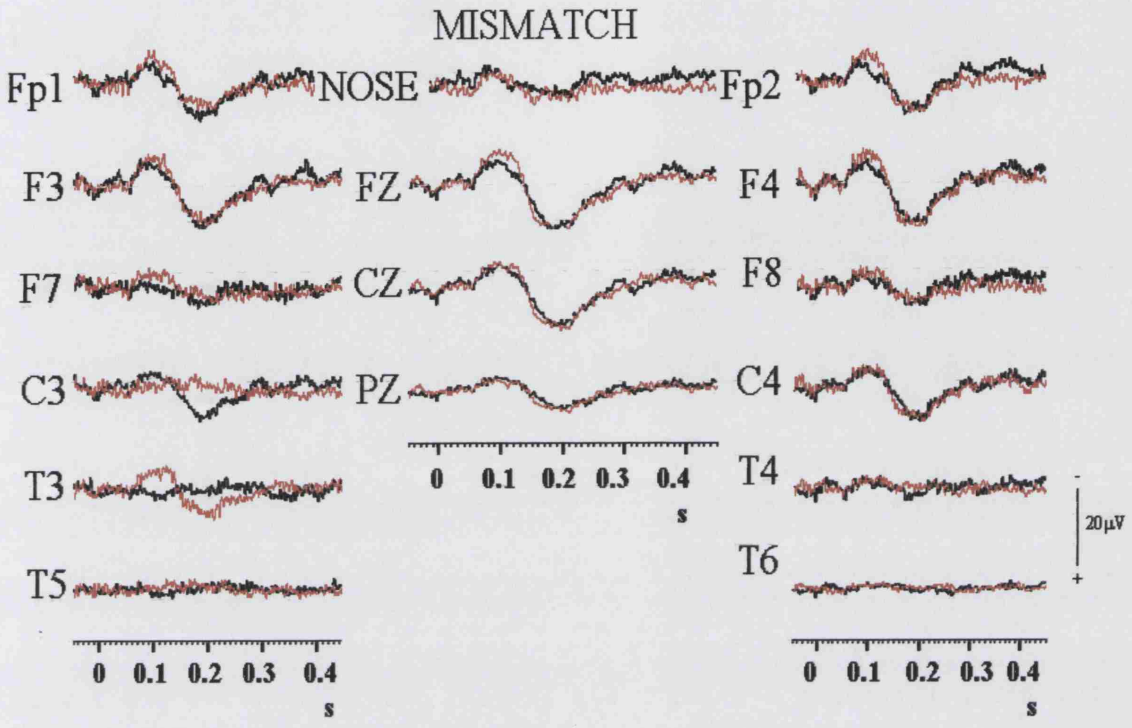

Fig. 3.28 Mismatch responses separated by 6 months from a normal control subject (n9). The second recording is represented in black.

For Onset, Frequency Change and Mismatch responses, latency values were obtained from electrodes over the right (F4) and left (F3) hemispheres. Amplitude values were obtained from F4 and C4 over the right and F3 and C3 over the left hemisphere. An amplitude ratio was calculated between the first and the second recording using the expression (x1-x2 / x1+x2). Mean values and normal limits of latency differences and amplitude ratios are seen in the Appendix.

Figures 3.29, 3.30 and 3.31 show average waveforms from the control subjects superimposed.

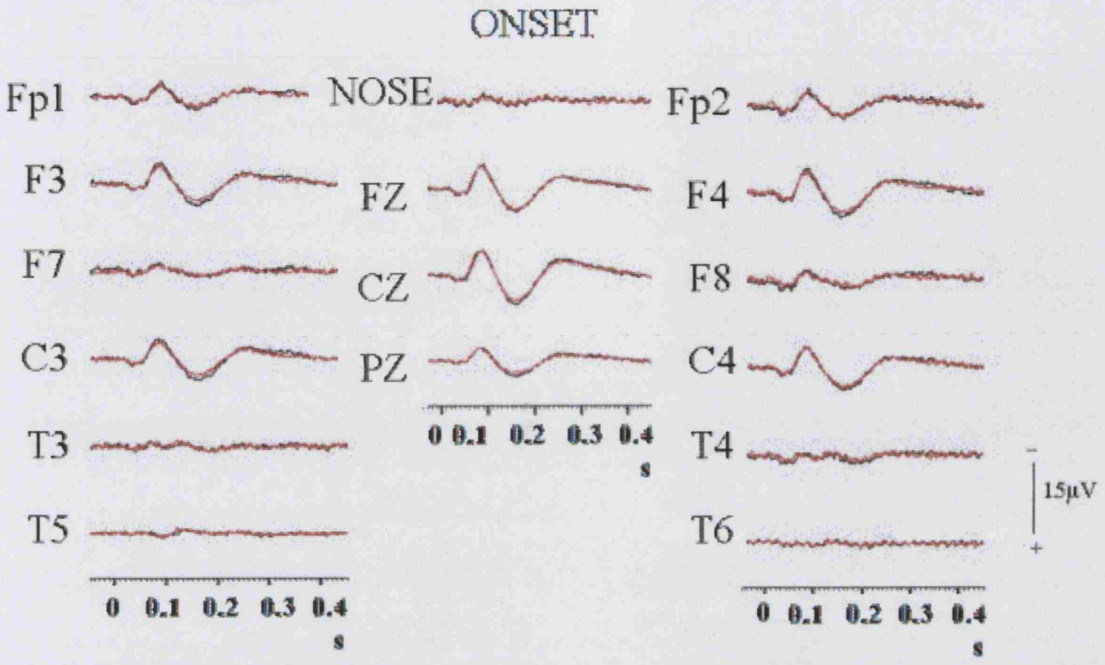

Fig.. 3.29 Superimposed responses from the first and the second recordings in a subgroup of fifteen normal subjects (Onset). The second recording is presented in black.

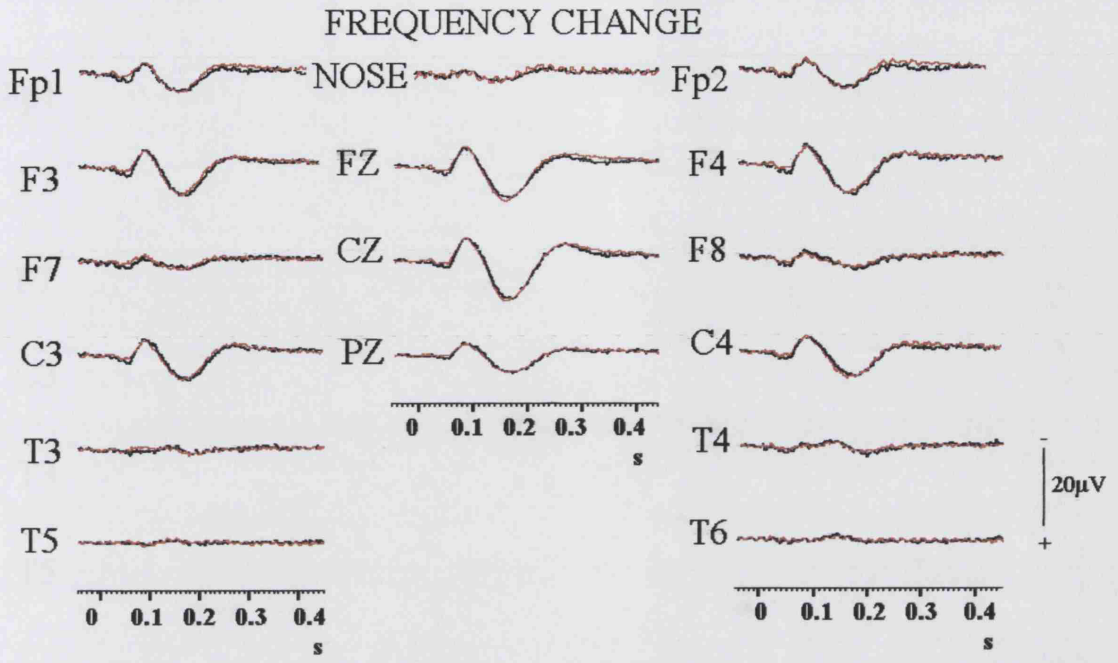

Fig. 3.30 Superimposed responses from the first and the second recordings in a subgroup of fifteen normal subjects (Frequency Change). The second recording is presented in black.

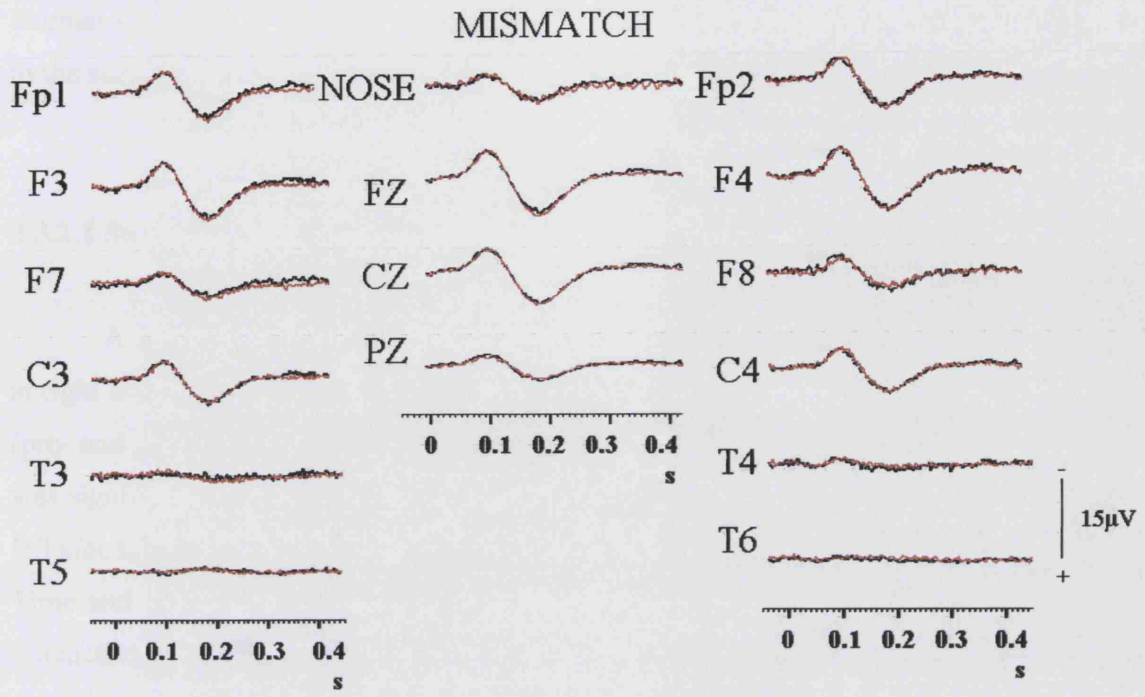

Fig. 3.31 Superimposed responses from the first and second recordings in a subgroup of fifteen normal subjects (Mismatch). The second recording is presented in black.

A serial evaluation was also performed for the T-complex. Results from the Onset response were not used for patient evaluation because the T-complex was present in less than 75% of the normal subjects. In Frequency Change responses, the T-complex was present in the first recording in 14 subjects on the right hemisphere and in 7 subjects on the left. In the second recording, responses were present in 14 subjects over the right hemisphere and in 13 subjects over the left. Only the right-sided results were used for patient evaluation, due to the small number of responses on the left hemisphere. The mean and normal limits of latency differences are presented in the Appendix.

3.3.2 Surgical patients

Forty-two patients were selected for surgery during the period of patient recruitment. Nineteen patients had right hippocampal sclerosis, 17 patients had left hippocampal sclerosis and 6 patients had non-hippocampal sclerosis lesions. Patients were evaluated before and after the surgical procedure, as described in Material and Methods.

Normal limits for serial changes obtained as described in the previous section were applied to the surgical patients' evoked potential data.

3.3.2.1 Surgical patients with right hippocampal sclerosis

A Repeated Measures ANOVA was performed in order to compare latency values at right and left electrodes, pre- and post-surgically. For ON1 the interaction between Time (pre- and post-surgical) and Side (right and left) was not significant, but Time Main Effect was significant ($F(1, 18) = 15.859$, $p=0.001$), suggesting a surgical effect on both right and left side ON1 latency, which was shorter post-surgically. No significant interaction between Time and Side, or any Main Effect of surgery was seen for OP2 latency. No significant interaction or Main Effect between Time (pre- and post-surgical) and Side (right and left) was seen for ON1 amplitude. For OP2 amplitude there was no Main Effect of surgery but there was a significant interaction between Time and Side ($F(1, 18) = 16.402$, $p=0.001$), due to a relative increase in amplitude post-surgically at right-sided electrodes.

There was no significant interaction (Time and Side) or Main Effect of Time for CN1 and CP2 latency between pre- and post-surgical values. CN1 amplitude showed a significant interaction between Time and Side ($F(1, 18) = 11.847$, $p=0.003$), with the right-sided values increasing and the left-sided values decreasing. CP2 amplitude showed no significant interaction (Time and Side) or Main Effect of Time.

MN1 and MP2 latency showed no significant (Side*Time) interaction or Main Effect of Time. MN1 amplitude showed a significant interaction between Time and Side ($F(1, 18) = 10.607$, $p=0.004$) due to relatively increased amplitude post-surgically on the right and a slight decrease on the left. MP2 amplitude did not show any significant Time and Side interaction or Main Effect of Time

The following MR images show pre- and post-surgical views from one patient of the right hippocampal subgroup. They show a pre-surgical view (Base), followed by a post-surgical sagittal view, a post-surgical coronal view and a subtraction between pre- and post-surgical images. Vertical traces represent the slice location for sagittal and coronal views. The surgical procedure was carried out with an anterior temporal lobe resection, removing about 3.5 to 4 centimetres of the lateral neocortex and approximately 3 centimetres of the

hippocampus. The extent of the removal of the anterior hippocampus and the amygdala within the uncus was dependent of the surgical access.

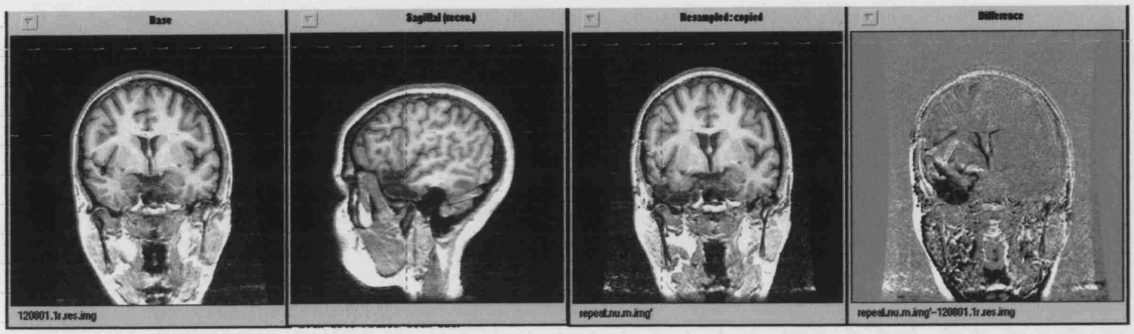

Fig. 3.32 MR images from patient 11, a female with right hippocampal sclerosis and 20y of disease, showing the pre- and post-surgical images.

Patients were also evaluated in an individual basis before and after surgical procedure. Figures 3.33, 3.34 and 3.35 presents the average responses before and after surgery from patient 11.

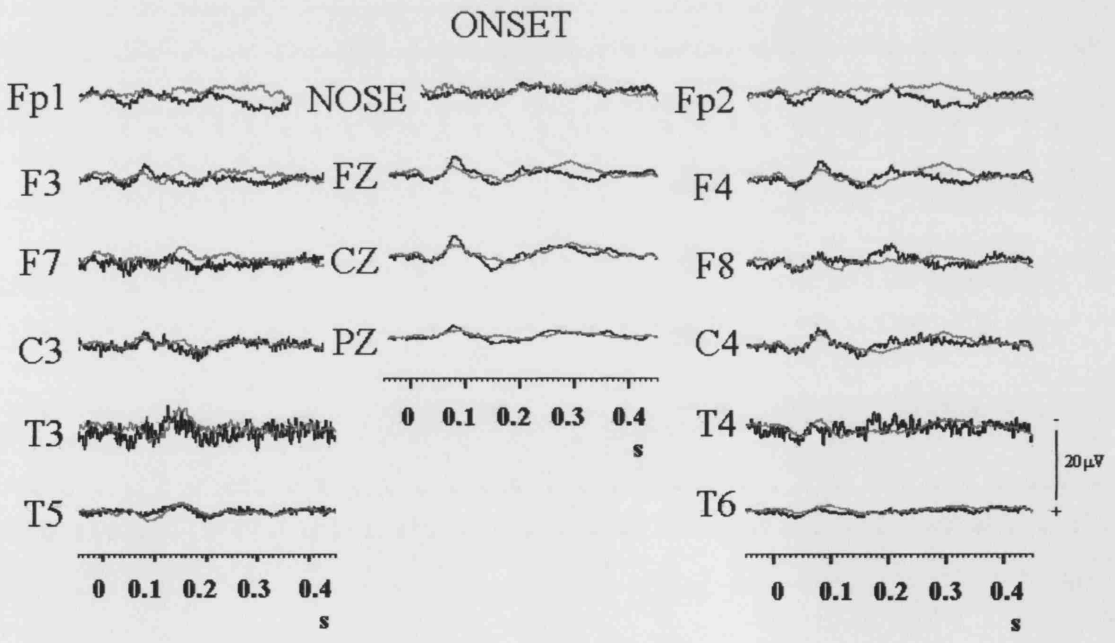

Fig 3.33 Pre- and post-surgical Onset responses from patient 11, pre-surgical responses shown in black. After surgery ON1 and OP2 are delayed over the left hemisphere, ON1 is larger over the left hemisphere and OP2 is smaller over the right hemisphere, when compared with the serial variation limits obtained from the control group.

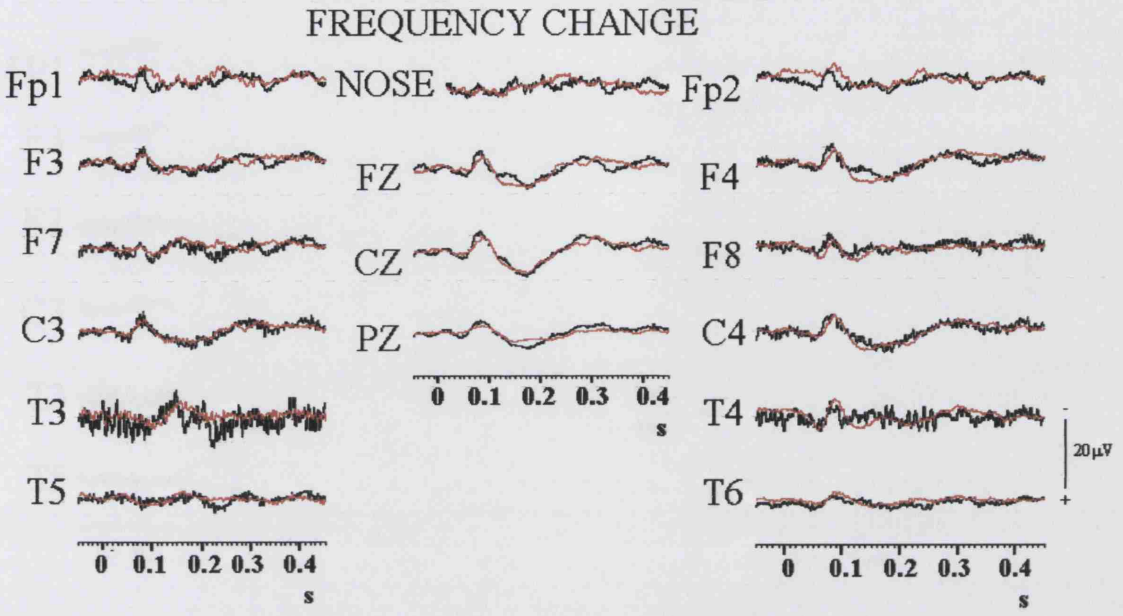

Fig. 3.34 Pre- and post-surgical Frequency Change responses from patient 11, pre-surgical responses shown in black. No significant differences are present after surgery when compared with the limits obtained from the control group.

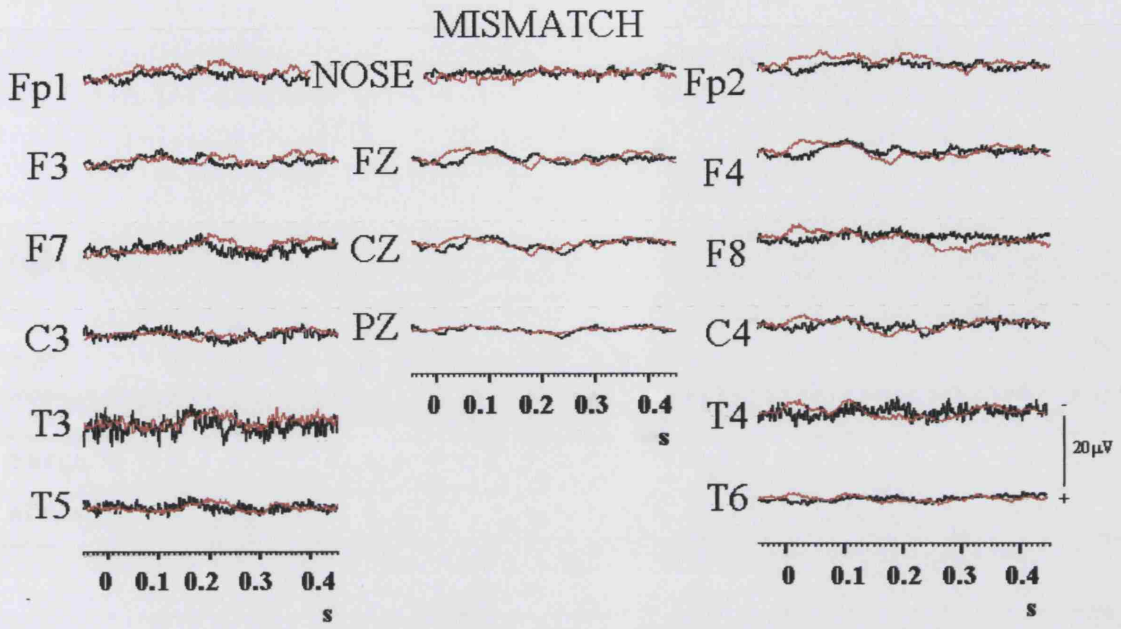

Fig. 3.35. Pre- and post-surgical Mismatch responses from patient 11, pre-surgical responses shown in black. After surgery MN1 and MP2 occur earlier over the left hemisphere, while MP2 is smaller at the left- and larger at the right-sided electrodes when compared with the serial variation limits obtained from the control group.

Table 3.8: Pre- and post-surgical mean latency for the right hippocampal sclerosis subgroup

Mean latency	N1 pre-surgical		P2 pre-surgical		N1 post-surgical		P2 post-surgical	
	Right	Left	Right	Left	Right	Left	Right	left
Onset	96.5	94.7	164.8	175.4	85.2	87.5	170.2	170.6
Fr. Change	93.8	92.3	173.1	176.2	84.4	84.7	168.8	172.7
Mismatch	109.0	102.5	195.1	184.9	92.7	107.7	182.0	196.6

Table 3.9: Pre- and post-surgical mean amplitude for the right hippocampal sclerosis subgroup

Mean amplitude	N1 pre-surgical		P2 pre-surgical		N1 post-surgical		P2 post-surgical	
	Right	Left	Right	Left	Right	Left	Right	Left
Onset	5.32	4.87	2.01	3.00	4.23	5.18	3.0	3.20

Fr. Change	4.95	5.33	4.08	4.61	5.97	4.71	4.56	3.47
Mismatch	4.67	5.14	3.19	2.77	5.67	4.80	3.92	2.95

Table 3.10 compares the number of abnormalities pre- and post-surgically for the right hippocampal sclerosis subgroup

Table 3.10: Incidence of evoked potential abnormalities for pre- and post-surgical assessment (surgical right hippocampal sclerosis subgroup)

Surgical right hippocampal sclerosis subgroup abnormalities	**Number of abnormal subjects**		
	Pre-surgical	Post-surgical	χ^2
Overall incidence of abnormalities	16/19	19/19	NS
Right-sided abnormalities	13/19	10/19	NS
Left-sided abnormalities	14/19	17/19	NS
Onset response abnormalities	15/19	18/19	NS
Frequency Change response abnormalities	14/19	11/19	NS
Mismatch response abnormalities	10/19	12/19	NS
N1 abnormalities	14/19	4/19	p=0.001
P2 abnormalities	12/19	17/19	NS
Latency abnormalities	13/19	12/19	NS
Amplitude abnormalities	10/19	11/19	NS
---	---	---	---
Mean incidence of abnormalities per patient (x/13)	3.52	2.47	

χ^2 tests comparing the number of abnormalities in the larger pre-surgical subgroup, from which these patients were drawn, and the smaller pre-surgical subgroup showed no significant difference either in the incidence of patients with abnormalities for each category or in the number of abnormal auditory evoked potential measures per patient ($p<0.005$). Differences between the number of subjects with pre- and post-surgical

abnormalities were not significant, except for the number of N1 abnormalities, which was smaller after surgery (p=0.001). The Wilcoxon test comparing the mean number of abnormalities per patient between the pre- and post-surgically responses was not significant (p<0.005).

Figures 3.36, 3.37 and 3.38 present the mean responses from the right hippocampal sclerosis surgical subgroup before and after surgery.

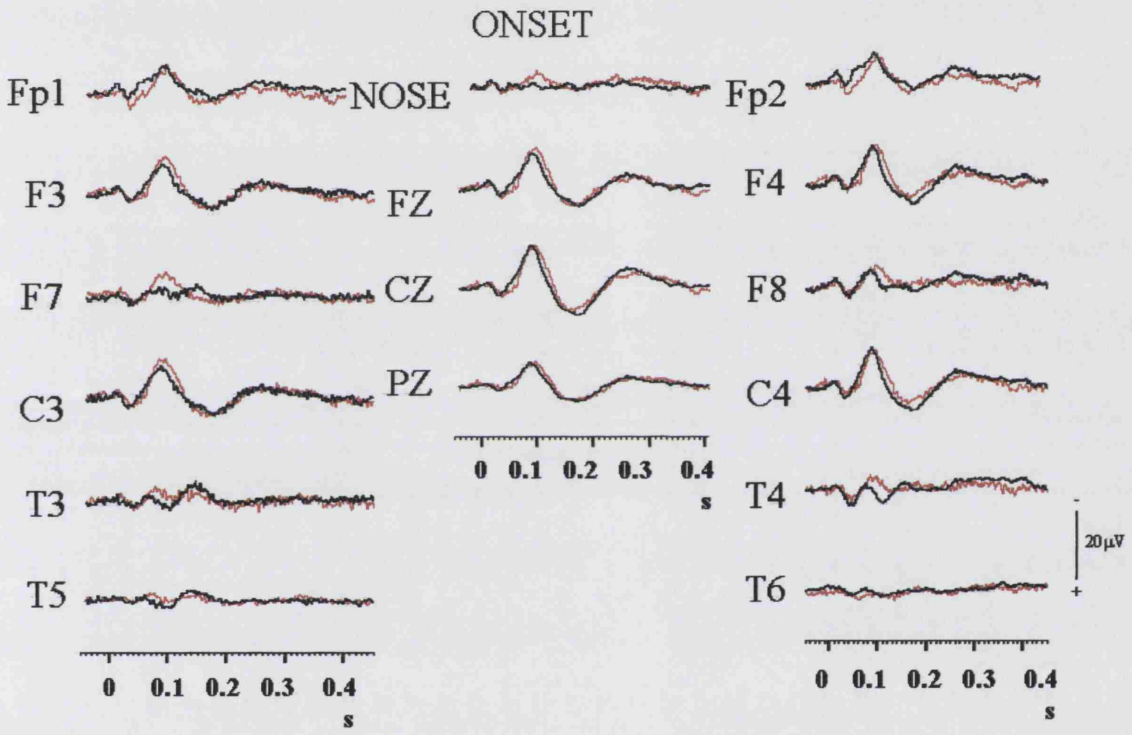

Fig. 3.36 Mean Onset pre- and post-surgical waveforms for the right hippocampal sclerosis surgical subgroup. Post-surgical recordings are shown in black. ON1 latency was shorter bilaterally and OP2 amplitude was increased over the right hemisphere and decreased over the left hemisphere after surgery.

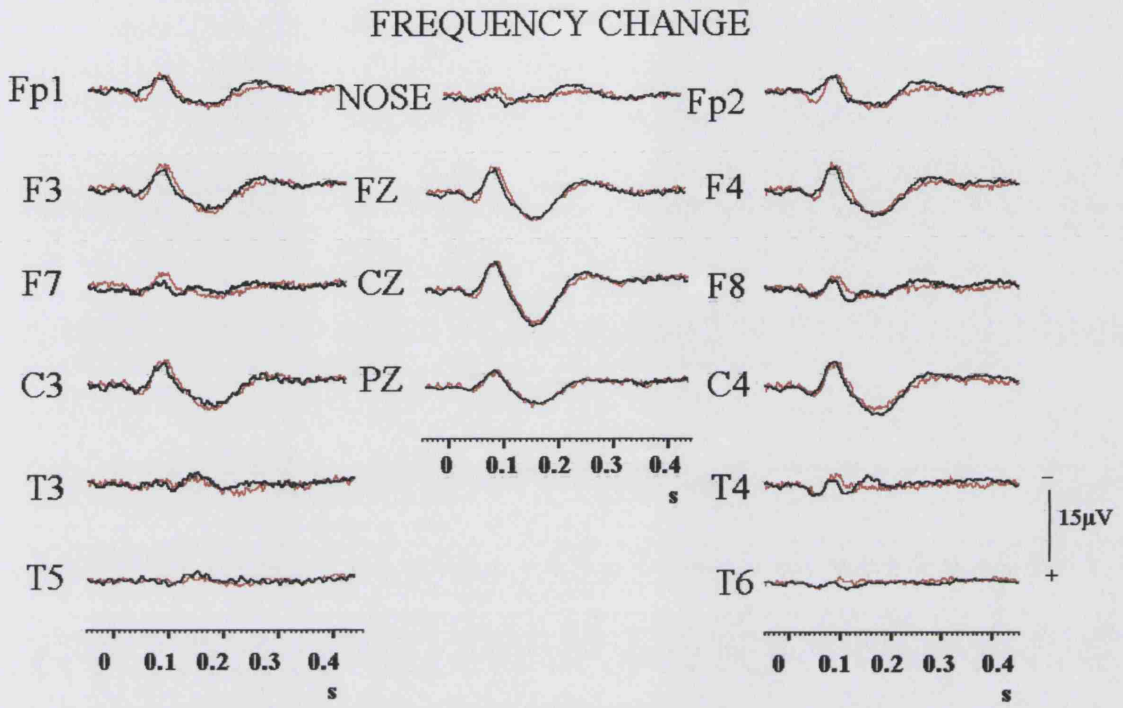

Fig. 3.37 Mean Frequency Change pre- and post-surgical waveforms for the right hippocampal sclerosis surgical subgroup. Post-surgical recordings are shown in black. CN1 amplitude was relatively increased on the right hemisphere and decreased on the left hemisphere after surgery

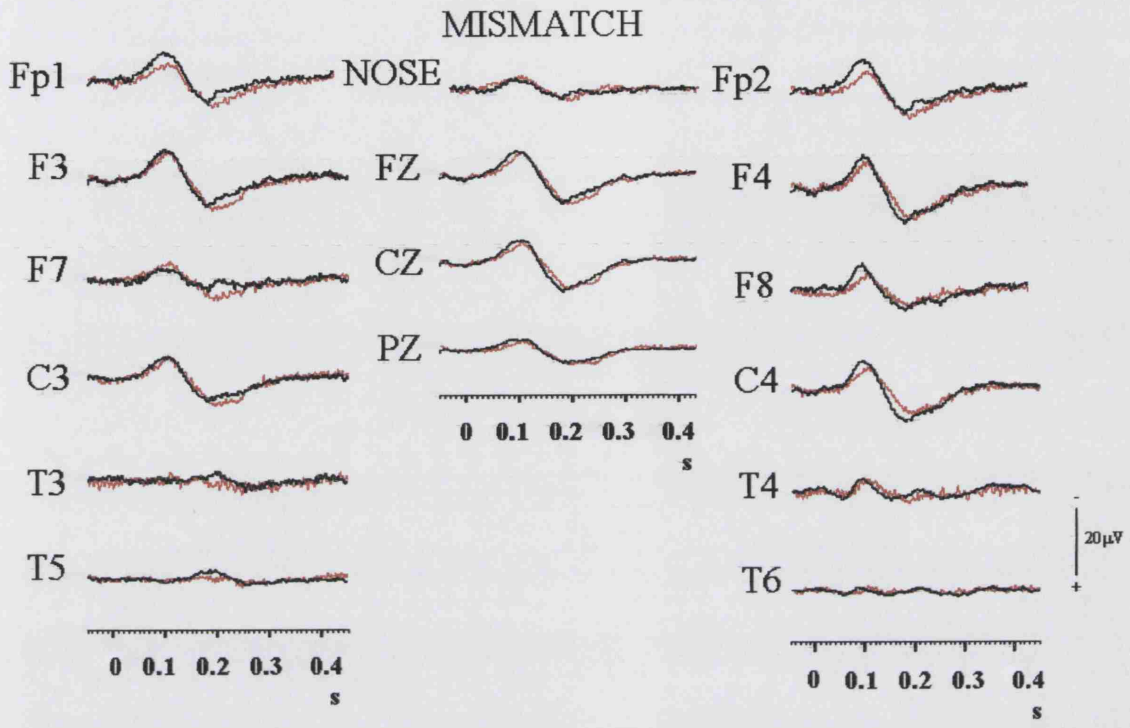

Fig. 3.38 Mean Mismatch pre- and post-surgical waveforms for the right hippocampal sclerosis surgical subgroup. Post-surgical recordings are shown in black. MN1 amplitude was relatively increased on the right hemisphere and decreased on the left hemisphere after surgery.

3.3.2.2 Surgical patients with left hippocampal sclerosis (n= 17)

Repeated Measures ANOVA was performed in order to compare latency at right and left electrodes, pre- and post-surgically. For ON1 the interaction between Time (pre- and post-surgically) and Side (right and left) was not significant, but Time Main Effect was significant ($F(1,16) = 11.427$, $p<0.005$), suggesting a surgical effect on both right and left side ON1 latency, which was shorter post-surgically. No significant interaction or Main Effect was seen for OP2 latency between pre- and post-surgical values. Repeated Measures ANOVA for ON1 and OP2 amplitude did not show any significant (Time*Side) interaction or Time Main Effect.

There was no significant (Time*Side) interaction or Main Effect of Time for CN1 and CP2 latency or amplitude.

MN1 latency did not show any significant interaction between Side (right and left)* Condition (pre- and post-surgical), but a significant Main Effect for Side was present ($F(1, 16) = 13.331$, $p < 0.005$), with left side latencies being significantly shorter than right side latencies before and after surgery. No significant Time Main Effect was found for MN1/MP2 amplitude values after surgery

The following MR images show pre- and post-surgical views from patient A12 of the left hippocampal subgroup, an ambidextrous male with left hippocampal sclerosis and 20 years of uncontrolled seizures. They show a pre-surgical view (Base), followed by a post-surgical sagittal view, a post-surgical coronal view and a subtraction view between pre- and post-surgical images. Vertical traces represent the slice location for sagittal and coronal views.

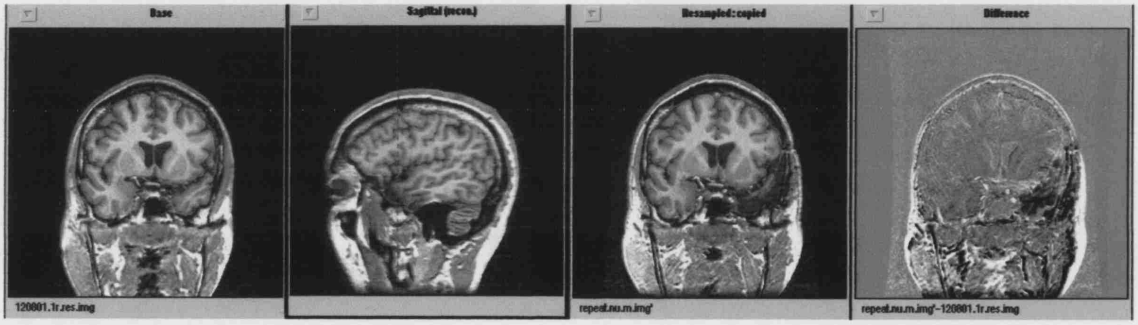

Fig. 3.39 MR images from patient A12, showing the pre- and post-surgical images described in the text.

Patients' auditory evoked potentials were evaluated on an individual basis before and after the surgical procedure. Figure 3.40, 3.41 and 3.42 present the average responses before and after surgery from patient A12.

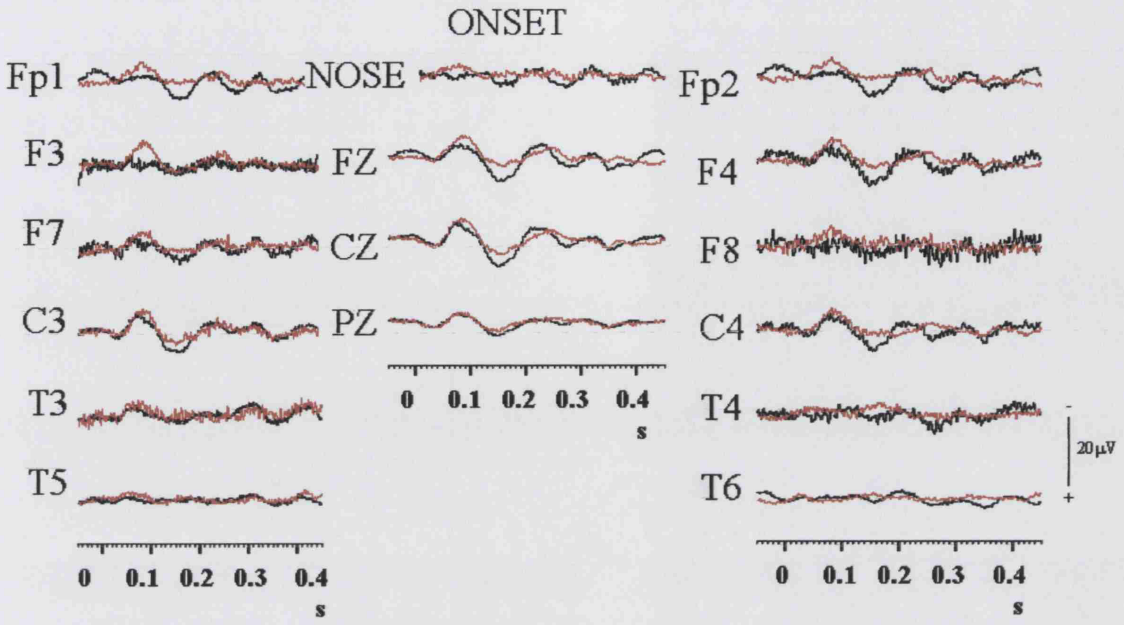

Fig. 3.40 Pre- and post- surgical Onset responses from patient A12, pre-surgical responses shown in black. After surgery, OP2 is smaller over the right hemisphere when compared with the serial variation limits obtained from the control group.

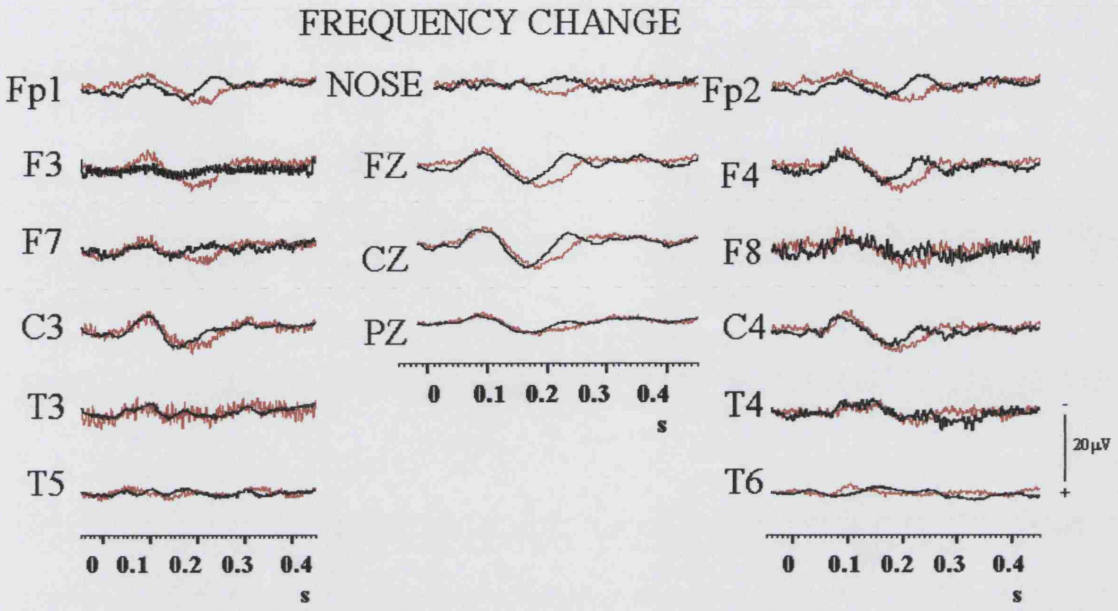

Fig. 3.41 Pre- and post-surgical Frequency Change responses from patient A12, pre-surgical responses shown in black. After surgery CN1 is smaller at the right electrodes, when compared with the serial variation limits obtained from the control group.

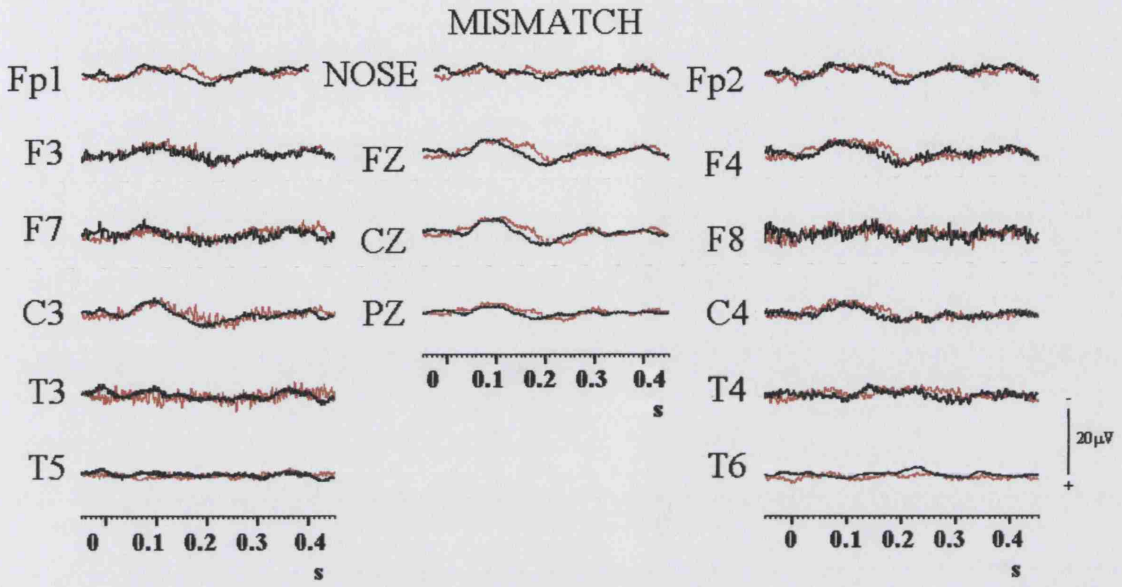

Fig. 3.42 Pre- and post-surgical Mismatch responses from patient A12, pre-surgical responses shown in black. After surgery MN1 and MP2 are delayed over the left hemisphere, while MP2 is smaller over the left hemisphere, when compared with the serial variation limits obtained from the control group.

Table 3.11: Pre- and post-surgical mean latency for the left hippocampal sclerosis subgroup

Mean latency	N1 pre-surgical		P2 pre-surgical		N1 post-surgical		P2 post-surgical	
	Right	Left	Right	Left	Right	Left	Right	Left
Onset	90.0	90.2	177.2	178.0	83.6	83.2	179.5	166.5
Fr. Change	88.4	87.1	173.9	172.6	88.5	88.9	173.6	170.2
Mismatch	102.5	99.0	206.7	196.4	105.8	101.9	200.4	190.6

Table 3.12: Pre- and post-surgical mean amplitude for the left hippocampal sclerosis subgroup

Mean amplitude	N1 pre-surgical		P2 pre-surgical		N1 post-surgical		P2 post-surgical	
	Right	Left	Right	Left	Right	Left	Right	Left
Onset	5.32	4.87	2.01	2.87	4.23	5.18	3.00	3.20
Fr. Change	5.24	4.96	4.24	4.99	4.69	4.98	4.50	4.41

Mismatch	5.53	3.70	5.38	3.36	4.45	4.63	4.66	4.19

Table 3.13 compares the number of abnormalities pre- and post-surgically for the left hippocampal sclerosis subgroup

Table 3.13 Incidence of evoked potential abnormalities for pre- and post-surgical assessment (surgical left hippocampal sclerosis subgroup)

Surgical left hippocampal sclerosis abnormalities	**Number of abnormal subjects**		
	Pre-surgical	Post-surgical	χ^2
Overall incidence of abnormalities	16/17	16/17	NS
Right-sided abnormalities	13/17	12/17	NS
Left-sided abnormalities	13/17	10/17	NS
Onset response abnormalities	12/17	11/17	NS
Frequency Change response abnormalities	12/17	12/17	NS
Mismatch response abnormalities	12/17	10/17	NS
N1 abnormalities	6/17	6/17	NS
P2 abnormalities	14/17	11/17	NS
Latency abnormalities	11/17	12/17	NS
Amplitude abnormalities	10/17	8/17	NS
Mean incidence of abnormalities per patient (x/13)	3.2	3.4	

χ^2 tests comparing the number of patients with abnormalities for each category between the larger pre-surgical left hippocampal sclerosis and the smaller surgical left hippocampal sclerosis subgroup were not significant and neither were there any significant differences in the incidence of abnormalities pre- and post surgically ($p<0.005$). The Wilcoxon signed rank test comparing pre- and post-surgical mean abnormalities was not significant ($p<0.005$).

Figures 3.43, 3.44 and 3.45 present the responses from the left hippocampal sclerosis subgroup before and after surgery.

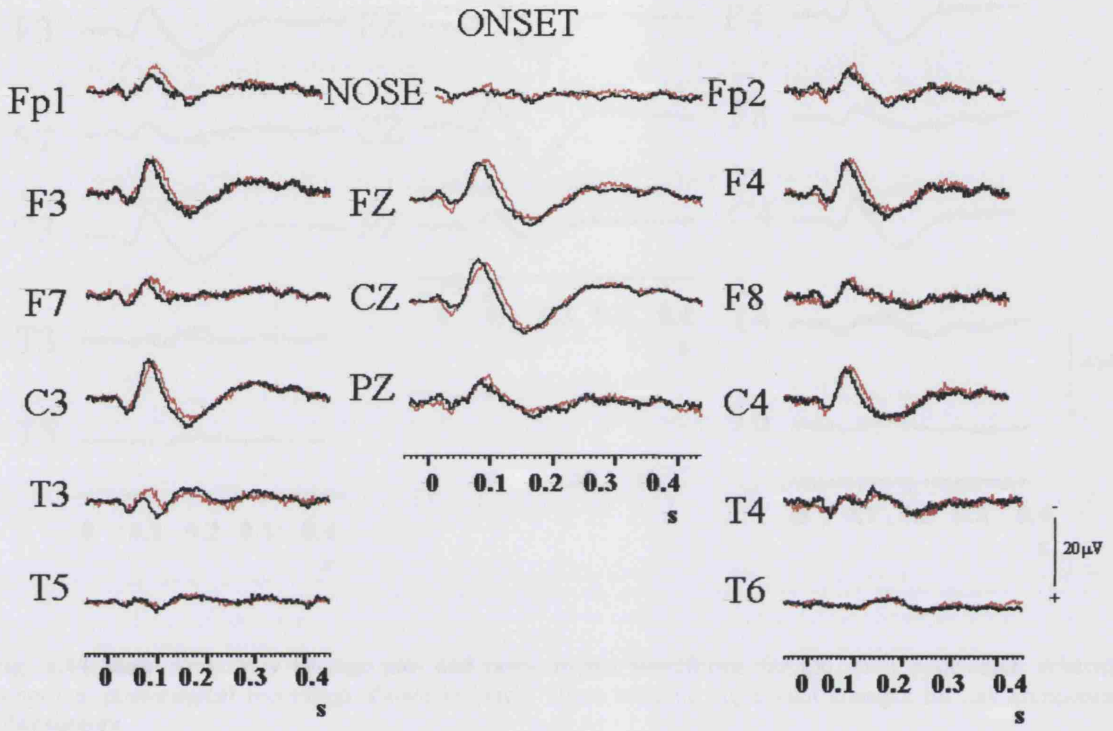

Fig. 3.43 Mean Onset pre- and post-surgical waveforms for the left hippocampal sclerosis subgroup, post-surgical recordings shown in black. After surgery ON1 latency was shorter in both hemispheres when compared with the pre surgical recordings.

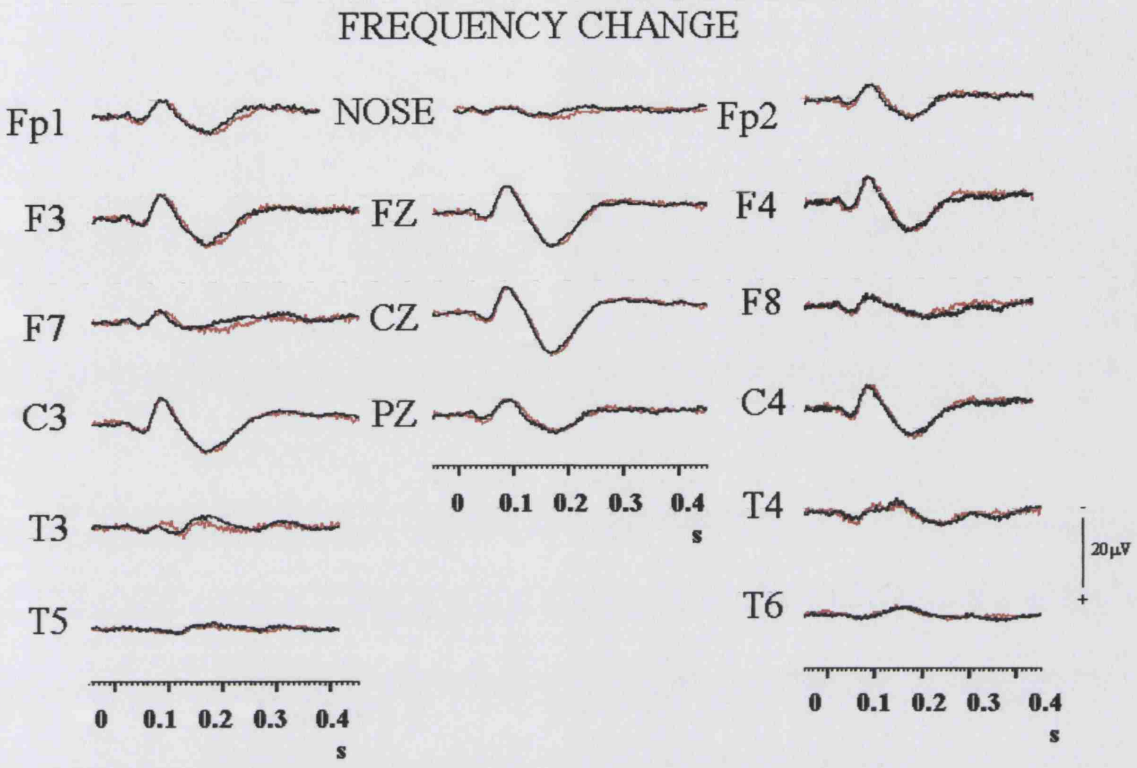

Fig. 3.44 Mean Frequency Change pre- and post-surgical waveforms for the left hippocampal sclerosis subgroup, post-surgical recordings shown in black. There were no significant changes for any component after surgery.

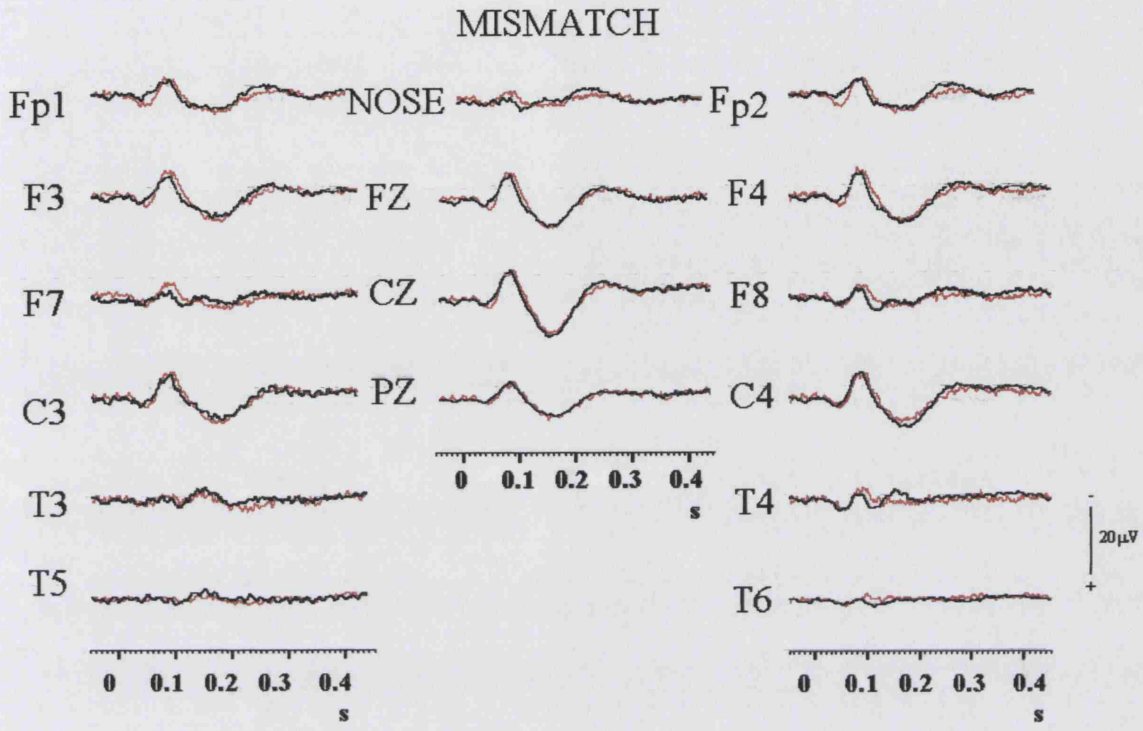

Fig. 3.45 Mean Mismatch pre- and post-surgical waveforms for the left hippocampal sclerosis subgroup, post-surgical recordings shown in black. MN1 and MP2 latencies were shorter over the left hemisphere, before and after surgery.

3.3.2.3. Non-hippocampal sclerosis subgroup

Only six patients from the non-hippocampal sclerosis subgroup had auditory evoked potentials recorded before and after surgery. No significant changes were observed

3.3.3 Serial evaluation of surgical changes

Improvement or deterioration of auditory evoked potentials was acknowledged when post-surgical change in response amplitude or latency exceeded the normal limits of serial changes.

Table 3.14 and 3.15 describe the incidence of post-surgical changes in the right and left hippocampal sclerosis subgroup.

Table 3.14. Incidence of patients with abnormal changes after surgery (right hippocampal sclerosis subgroup)

Right hippocampal sclerosis abnormal changes after surgery	Improved	Deteriorated	Mixed
Overall incidence of changes	2	2	14
Ipsilateral changes	4	4	9
Contralateral changes	3	4	10
Onset changes	6	1	7
Fr. Change changes	6	2	3
Mismatch changes	2	5	8
N1 changes	8	1	5
P2 changes	3	7	8
Latency changes	5	2	10
Amplitude changes	2	5	6

Table 3.15 Incidence of patients with abnormal changes after surgery (left hippocampal sclerosis subgroup)

Left hippocampal sclerosis abnormal changes after surgery	Improved	Deteriorated	Mixed
Overall incidence of changes	3	2	11
Contralateral changes	2	2	8
Ipsilateral changes	5	3	7
Onset changes	4	3	4
Fr. Change changes	2	4	1
Mismatch changes	7	1	4
N1 changes	6	1	5
P2 changes	5	4	6
Latency changes	5	2	7
Amplitude changes	4	5	2

In most patients of both hippocampal sclerosis subgroups the changes were mixed. There were no significant differences in the incidence of improved as compared with deteriorated responses. Onset and Frequency Change responses showed a slight tendency to

improve in the right hippocampal sclerosis subgroup, while Mismatch responses tended to improve in the left hippocampal sclerosis subgroup. The N1 showed a fairly strong tendency to improve in both subgroups, while effects on the P2 were mixed. Latency measures showed a slight overall tendency to improve while amplitude measures tended marginally to deteriorated

3.4 Relationship between neuropsychological surgical changes and evoked potentials surgical changes

Methodology for serial evaluation of evoked potentials and Neuropsychology was explained in Material and Methods. In summary, a correlation was obtained between the difference of pre-surgical and post-surgical neuropsychological mean scores and the difference of pre-surgical and post-surgical evoked potential latencies and the ratio of pre-surgical and post-surgical evoked potential amplitudes.

Three patients from the surgical left hippocampal sclerosis subgroup did not perform the two parts of the neuropsychological evaluation and were not included, nor were 3 patients from the surgical non-hippocampal sclerosis subgroup and 3 patients from the surgical right hippocampal sclerosis subgroup. The surgical non-hippocampal sclerosis subgroup was not considered here owing to the small number of subjects evaluated.

Table 3.21 presents the mean pre-surgical and post-surgical neuropsychological scores for the surgical right hippocampal sclerosis subgroup (n=16) and the surgical left hippocampal sclerosis subgroup (n=14).

Table 3.16: Mean pre- and post-surgical neuropsychological scores (H.S. = hippocampal sclerosis)

	STORY		FIGURE		LIST		DESIGN		WORD	
	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-	Pre-	Post-
	Mean/ S.D.	Mean/ S.D.	Mean/ S.D.	Mean/ S.D.	Mean/ S.D.	Mean/ S.D.	Mean/ S.D.	Mean/ S.D.	Mean/ S.D.	Mean/ S.D.
Right H.S.	40.1/ 17.3	33.0/ 17.1	74.3/ 21.4	69.8/ 26.7	15.6/ 4.1	13.1/ 5.2	12.7/ 3.4	10.8/ 5.8	14.5/ 6.5	15.9/ 9.3
Left H.S.	29.4/ 22.7	28.5/ 17.8	68.7/ 28.6	72.4/ 27.9	12.1/ 5.5	11.3/ 5.2	11.3/ 4.6	11.8/ 4.7	12.5/ 6.3	13.1/ 8.8

Table 3.17 presents the number of patients showing increase/reduction in the mean scores after surgery. One patient from the surgical right hippocampal sclerosis subgroup had the same mean score for "Story" before and after surgery and three patients from the same subgroup had the same score for "Design". In the left hippocampal sclerosis subgroup, one patient had the same mean score before and after surgery for "Story" and another patient had the same mean score before and after surgery for "Design".

Table 3.17: Number of patients showing increase/ reduction neuropsychological scores after surgery (+=improved,-= deteriorated, = maintained, HS= hippocampal sclerosis)

	Story		**Figure**		**List**		**Design**		**Word**	
	+	-	+	-	+	-	+	-	+	-
Surgical right HS subgroup	10	5 (1=)	11	5	6	10	6	7 (3=)	11	5
Surgical left HS subgroup	6	7 (1=)	8	6	6	8	9	4 (1=)	6	8

Correlations obtained to all patients showed a positive correlation between the surgical variation of ON1 amplitude at the right electrodes and the surgical variation of the scores for "Figure" (Pearson's correlation value=0.55, p =0.001).

No significant correlations ($p<0.005$) were seen for Frequency Change.

For Mismatch, a positive correlation was seen between the surgical variation of MN1 latency at the right electrodes and the surgical variation of scores for "Design" (Pearson's correlation value=0.58, p=0.001) but the exclusion of an extreme value (outlier) made it not significant.

The presence of a positive correlation between all patients' values and neuropsychological tests suggested the possible presence of positive correlations between each subgroup, and each subgroup of patients was evaluated per se.

3.4.1 Surgical subgroup with right hippocampal sclerosis (n=18)

Table 3.18 shows the results for the correlation tests performed between the difference of pre- and post-surgical auditory evoked potentials and the difference of mean scores of the Neuropsychological tests, before and after surgery.

Table 3.18 Correlation tests between post-surgical changes in evoked potentials and neuropsychological test score changes in the right hippocampal sclerosis subgroup.

	ONSET	FREQUENCY CHANGE	MISMATCH
N1 R lat.			***Design (+), R= 0.69***
P2 R lat.			
N1 L lat.			
P2 L lat.		***Design (-), R=-0.66***	
N1 R amp.	***Figure (+), R= 0.67***		
P2 R amp.		***Word (-), R = -0.77***	
N1 L amp.			
P2 L amp.			

R= Pearson Correlation Coefficient

The surgical right hippocampal sclerosis subgroup showed a positive correlation between changes in ON1 amplitude at the right electrodes and changes in Figure scores ($p=0.001$). A negative correlation between changes in CP2 amplitude at the right electrodes and changes in "Word" scores was significant as was a negative correlation between changes in CP2 latency at the left electrodes and changes in "Design" scores ($p<0.005$). However, the exclusion of an extreme value (outlier) made them not significant. There was also a positive correlation between changes in MN1 latency at the right electrodes and changes in "Design" scores but the exclusion of an extreme value (outlier) made it not significant.

3.4.2 Surgical subgroup with left hippocampal sclerosis (n=14)

No significant correlations were seen between evoked potential and neuropsychological surgical changes in this subgroup.

3.5. Evaluation of the relationship between surgical changes in auditory evoked potentials and surgical resection volume

The surgical resection volume was obtained as described in Material and Methods. Values were correlated with changes between pre- and post-surgical auditory evoked potential measurements.

Six patients from the surgical left hippocampal sclerosis as well as 2 from the surgical non-hippocampal sclerosis subgroup and 4 patients from the surgical right hippocampal sclerosis subgroup did not have the post-surgical MRI scan at the time of the measurements. Surgical non-hippocampal sclerosis subgroup was not considered for this evaluation due to the small number of patients to be evaluated.

Table 3.19: Mean values for volume resection

Volume (mm^3)	Mean/ S.D.
Right hippocampal sclerosis subgroup	16.2 / 7.7
Left hippocampal sclerosis subgroup	18.5/ 7.8
Non-hippocampal sclerosis subgroup	8.8/7.5

No significant correlation was seen for the volume of resection and surgical evoked potential changes for each of the subgroups considered.

Discussion

4.1 Primary objectives

The objective of the present work was to examine long-latency auditory evoked potentials in response to complex tones (ON1/OP2, CN1/CP2, MN1/MP2) in a population of patients undergoing surgery for temporal lobe epilepsy. The first hypothesis was that, due to the possible relationship between long-latency auditory evoked potentials, specifically the mismatch potentials and memory processes involving the hippocampus, the MN1/MP2 response might be different in a population of patients with hippocampal sclerosis as compared with a normal population. It was also hypothesised that this difference might be lateralized to the affected hemisphere. It was decided to evaluate the incidence of abnormalities in the pre-surgical group of patients and to determine whether they were more frequent on the side of the lesion. A significantly larger number of abnormalities per subject was present in each pre-surgical subgroup when compared with the normal control group. The comparison between the normal control group and the pre-surgical subgroups of patients showed a significantly longer latency for one or more components for the Onset condition in the right and left hippocampal sclerosis and the normal MRI subgroups. One or more Mismatch components were also significantly delayed in latency in the Mismatch condition in all the patients' subgroups when compared with the normal control group. No significant latency differences were seen for Frequency Change condition, neither were there any significant effects on amplitude in any of the three conditions. No significant laterality effects were seen in amplitude or latency, amplitude ratios or latency difference between the lesioned and the normal hemisphere for each subgroup of patients. The findings therefore suggest a high incidence of delayed auditory evoked potentials in patients with long-standing epilepsy, but no specific relationship with epilepsy of hippocampal origin.

The second hypothesis was that the surgical procedure might interfere directly with the generators of these evoked potentials (presumed to be generated at or near the auditory cortex, in the supratemporal plane) or indirectly, due to the resection of the hippocampus, presumed by some authors (rev. by Alho, 1995) to be related to the generation of some long latency evoked potentials, particularly the MMN. Also, in view of the possible relationship between the MN1 and the MMN explained in the introduction, it was hypothesised that there might be surgical changes in the MN1 amplitude or latency. After surgery, the

number of subjects with abnormalities was not significantly different from the pre-surgical number of subjects with abnormalities in patients with right and left hippocampal sclerosis. Post-surgically, the ON1 response showed a bilateral decrease in latency for both subgroups with hippocampal sclerosis. OP2, CN1 and MN1 showed an altered inter-hemispheric amplitude ratio, with relatively increased amplitude ipsilateraly to the surgical resection and a suggestion of decreased amplitude contralateraly in the right hippocampal sclerosis subgroup. Moreover, after surgery, there was a significantly reduced incidence of abnormalities for the N1 component in the right hippocampal sclerosis subgroup. Although on average a larger number of evoked potential measures improved, most subjects presented with mixed responses (improved and deteriorated measures simultaneously). The overall effect of surgery therefore was not to cause any increase in the incidence of auditory evoked potential abnormalities but (for patients with right hippocampal sclerosis) possibly to increase the activity of the auditory cortex adjacent to the damaged hippocampus.

A third hypothesis of this work was that, due to the possible relationship between CN1/CP2 and MN1/MP2 and the echoic memory outlined in the Introduction, there might be some correlation between post-surgical changes in the evoked potentials and changes in neuropsychological test scores, owing to the possible subserving role of the echoic memory with the working memory. A significant correlation between surgical changes in ON1 amplitude on the right side of the head and Figure scores was observed in the right hippocampal sclerosis subgroup, suggesting a similar effect of surgery for both measures. Although a p value of 0.005 was applied, it is not possible to exclude a type I error completely.

4.2 – *What is the nature and likely cause of auditory evoked potential abnormalities in patients with temporal lobe epilepsy due to hippocampal sclerosis?*

The overall incidence of auditory evoked potential abnormalities was very high in all the subgroups and in all the components considered in the pre-surgical tests. The subgroup with right hippocampal sclerosis showed abnormalities in 95.4% of the subjects with a mean number of abnormal components per patient (N1 right and left in amplitude and/or latency, P2 right and left in amplitude and/or latency evaluated for the three stimulus conditions, and the latency of the T-complex for Frequency Change) of 5.8. The subgroup with left hippocampal sclerosis showed abnormalities in 98.2% of the subjects, with a

higher mean number of abnormal components per patient (8.8). The subgroup with no MRI lesions showed 100% of abnormal subjects and a mean of 4.5 abnormal components per patient. The subgroup with right, left and bilateral lesions that were not hippocampal sclerosis showed 91.7 to 100% of abnormal subjects, with a mean of abnormal components per patient varying from 2.9 to 5.6. The much lower incidence of "abnormal" components per subject in the normal control group (0.13) and the similar large number of abnormal components present in all patient subgroups in spite of the different location of the lesions suggest a common mechanism in the disruption of auditory responses.

In order to evaluate this, the findings in the subgroup with no visible MRI lesions are crucial as these patients showed epilepsy with origin in the temporal lobe, but with no apparent structural lesions. The incidence of abnormalities (100%) was not significantly different from the incidence of abnormalities in the subgroup with hippocampal sclerosis (95.4 to 98.2%), or the subgroups with other lesions (91.7-100%). Subgroups with right and left-sided lesions other than hippocampal sclerosis had different types of macroscopic lesions in the temporal lobe and elsewhere, while the subgroup with bilateral lesions was mostly characterised by patients with dispersed lesions, mainly in the white matter and /or frontal lobes. Additionally, the comparison of the pre-surgical subgroups in a multivariate ANOVA showed no significant differences for the amplitude or latency of any component in any condition. Therefore, the location of macroscopic lesions or the presence of hippocampal sclerosis did not seem to influence the incidence of long latency auditory evoked potential abnormalities in these patients. This diversity of anatomical locations and types of lesions suggests that the auditory evoked potential abnormalities are probably related to the characteristics of the disease common to all groups, such as a long-standing history of uncontrolled complex partial epilepsy, with prolonged use of more than 2 anti-epileptic drugs per day. The subgroups were not statistically different regarding these characteristics (excepting that patients with hippocampal sclerosis showed a significantly longer history of disease), and this could explain the similar percentages of abnormalities observed.

Although most studies of event-related potentials in temporal lobe epilepsy were not directed towards pre-attentive auditory responses, their results tend to reflect similar findings. In fact the majority of previous work was directed towards the P300 and later potentials, believed to be a reflection of short-term memory and consequently related with the hippocampal formation and working memory. Caravaglios et al. (2001) showed delayed

latency of the P300 in a population of uncontrolled epileptics (secondary and primary generalised epilepsy), which they related to epilepsy duration, seizure frequency and polytherapy. In the study by Ford et all, (2001) P300 and N1 were also abnormally delayed in a population of epileptic patients when compared with a normal group matched for age. Ford et all (2001) and Koseoglu and Karaman (2001) observed a similar incidence of abnormally delayed P300 in patients with idiopathic generalised epilepsy. Interestingly, the incidence of abnormal P300 was reduced three months later in the group of patients that used the medication effectively, possibly due to a better control of the seizures. Also in the present work there was no significant difference in the delay of the waveforms in the subgroups with or without macroscopic lesions, suggesting a lesser effect of the anatomical disruption and a larger functional effect of the uncontrolled epileptic seizures on the components.

P300, N2 and P2 latency were also significantly delayed in patients with cryptogenic partial epilepsy and idiopathic generalised epilepsy when compared with a control group, amplitudes also being lower in both groups of patients as compared with the control group (Soysal et al, 1999). Drake et al (1986) also reported delayed N2 and P300 responses in patients with controlled complex partial and secondary generalised seizures with no cerebral lesions. Overall, the evoked potential latencies in their epileptic patient population were significantly longer than in the normal control population.

The longer latency observed in the event related potentials reported here could also have other origin apart from hippocampal sclerosis, since the normal hippocampus on the other side of the brain could be sufficient to produce a normal response. Puce and Bladin (1989) found no P300 response ipsilateral to the sclerotic hippocampus from intracerebral recordings, while a normal P300 was present at the scalp electrodes. They suggested that it was possible that the normal hippocampus of the contralateral hemisphere could have been responsible to the normal scalp recordings. In another study, however, unilateral hippocampal damage was associated with a bilaterally reduced P300 to both targets and novel stimuli, suggesting the involvement of a bilateral facilitatory system based on or involving the hippocampus in the detection of the deviance and novelty (Knight, 1996). Due to the differences between the ON1, CN1 and MN1 responses compared with the P300, it is difficult to extrapolate any similar interpretation to these components. In the present work, the hippocampal effect did not appear in the pre-surgical evaluation, in so far as the differences between the hippocampal sclerosis subgroups and the non-hippocampal

sclerosis subgroups were not significant, suggesting that the sclerotic hippocampus effect was not important to the abnormalities present. A type II error cannot be excluded, due to the small p value considered significant. Also if the hippocampus does affect long-latency evoked potentials, the contralateral normal hippocampus in the pre-surgical population could have produced a normal evoked potential response.

However, if we envisage the occurrence of a seizure as an electrical disruption of normal brain function, associated with immediate changes and post-seizure effects in different neurotransmitters, it is understandable that high order sensory processing, probably involving widespread neural networks, can be disrupted by the occurrence of one or several seizures per day, as appears to be the case in the patients of the present study. It is known that the continued exposure to seizures, as happens in long-standing complex partial epilepsy, creates abnormal neural connections, specifically in the hippocampus (eg: Mouritzen Dam, 1992, rev. Mathern et al, 1995). This effect could account both for the abnormalities in the processing of sound and the observed abnormalities in the neuropsychological assessment of these patients.

The results of the pre-surgical assessment therefore suggest that the auditory evoked potential abnormalities are probably more related to a general dysfunction of auditory processes caused by epilepsy and/or anti-epileptic drugs than to specific brain lesions. No significant differences were recorded between right and left electrodes in any subgroup of patients. Therefore, one must conclude that the presence or absence of lesions did not influence the distribution of abnormalities over the right and left hemispheres. Knight et al (1988) demonstrated bilateral or ipsilateral reductions of N1 sub-components in patients with large lesions, due to cerebro-vascular accidents and tumour resection in the superior temporal gyrus and/or the inferior parietal lobe. In their review of 1987, Woods and collaborators mentioned conflicting results from previous literature but showed absent N1/P2 in patients with bilateral temporal lobe lesions with simultaneous involvement of the right parietal lobe. However, the presence of a normal N1/P2 in patients with unilateral temporal lesions (Woods et al., 1984), led the authors to suggest the need for more widespread involvement of the temporal cortex in order to cause waveform changes. In the present study, one possible reason for the absence of a lesional effect on the N1/P2 complex over and above the effect of seizures and/or anti-epileptic drugs could relate to the dimensions of the lesions concerned. Some patients of the non-hippocampal sclerosis subgroup had large lesions but these were not homogeneous in location (some lesions were

frontal, some were temporal) and thus consistent effects on the auditory evoked potentials might not be expected. Also, the hippocampal sclerosis patients showed only hippocampal lesions, mostly unilateral. The effect of the normal hippocampus, simultaneously with the adverse effects of concurrent factors could account for the non-lateralising effect of the lesions.

Together with the adverse effects of seizures and years of disease, as well as the underlying lesions, epileptic patients also suffer from iatrogenic effects that may be reflected in abnormalities of evoked potentials. In previous studies, N1 responses were delayed or attenuated in relation to the use of anti-epileptic drugs such as carbamazepine, clonazepam or phenytoin, with or without a delay in more peripheral responses (Akaho 1996, Drake et al, 1989) and improved after reduction of the anti-epileptic medication (Tuunainen et al, 1995). The characteristics of abnormalities in the present study are similar to those observed in these studies, also showing a predominance of delay in latency over reduction in amplitude. All patient subgroups in this study had a similar number of different anti-epileptic drugs consumed per day by each patient and, with the exception of the non-hippocampal sclerosis patients with left sided or bilateral lesions, all subgroups showed a greater number of latency abnormalities as compared with amplitude abnormalities. In accordance with our results, Bougeard and Fischer (2002) found a similar delay in the latency of Na, Pa, N1 and N200 and lower Pa amplitude in a group of patients with temporal lobe epilepsy and hippocampal sclerosis, prior to surgery. The small number of patients involved and the use of percentages makes any conclusion presumptive, but it is conceivable that the presence of bilateral lesions in the bilateral non-hippocampal sclerosis subgroup could result in a more severe disruption of networks, severe enough to reduce the number of neurons involved in sound assessment, reflected in the number of amplitude abnormalities.

The absence of a lateralised effect of lesions was assumed due to the fact that most comparisons between the patient pre-surgical subgroups were not statistically significant. This could be either because there were no actual differences between the subgroups or because the conservative p value used ($p<0.005$) resulted in a Type II error. It is possible that some differences between the subgroups of patients and between right- and left-sided electrodes were present but were not strong enough to be detected.

The greater number of right-sided auditory evoked potential abnormalities present in most pre-surgical patient groups (although not significant) is noteworthy. If we consider

the large number of reports on neuropsychological aspects and functional imaging of spectral and temporal analysis of sound (eg: Zatorre, 1988; Samson and Zatorre, 1994; Liegeois-Chauvel et al, 1998; Johnsrude et al, 2000), a right hemisphere preponderance is usually seen, both in lesional studies and in normal controls. Samson and Zatorre (1994) defined the right temporal lobe as the site of processing spectral and temporal information in sound, mostly for changes occurring slowly. Liegeois-Chauvel et al (2001), using intracerebral electrodes in humans, described a much more tonotopically organised right auditory cortex than the left auditory cortex, possibly related to a more precise and accurate spectral analysis. In the present study, the symmetrical distribution of the responses over both hemispheres in the normal control group does not support the idea that the right hemisphere is the more important one in the generation of ON1, CN1 and MN1. However, the higher incidence of auditory evoked potential abnormalities over the right hemisphere in most subgroups of patients could possibly suggest greater susceptibility of the right hemisphere to the pathological process and /or to the medication used by epileptic patients.

The P2 component showed more abnormalities than the N1 in all the subgroups. While the principal generator of N1 is believed to be located in the superior aspect of the temporal lobe (Näätänen and Picton, 1987), which was also confirmed by comparing intracerebral recordings with magnetoencephalography in humans (Godey et al, 2001), the location of P2 generator is less clear and the present study did not elucidate it. In the present study, the apparently higher sensitivity of the P2 component to the combination of factors that contribute to long latency auditory evoked potential abnormalities in epilepsy suggests a different functional aspect to this potential, possibly more complex and hierarchical than the N1 component.

The subgroup with normal MRI may be used as a template for the general effects of epilepsy and its treatment. In the Mismatch condition, disruption due to epileptic seizures and/or anti-epileptic drug administration produced abnormalities in 66.7% of patients with no lesions visible on MRI. A similar incidence of abnormalities was seen in the subgroup with right hippocampal sclerosis (67.4%), the subgroup with right-sided lesions that were not hippocampal sclerosis (66.7%) and the subgroup with bilateral lesions that were not hippocampal sclerosis (57.1%). The subgroups with left hippocampal sclerosis (80%) and with left-sided lesions that were not hippocampal sclerosis (98.3%) both showed a greater percentage of abnormalities as compared with the subgroup with normal MRI. Two points are noteworthy in these results. First, the general disruption associated only with long-

standing epilepsy and anti-epileptic drug use tended to affect fewer (10/15) subjects in the Mismatch condition than in Frequency Change (15/15) or in Onset (12/15) in the subgroup with normal MRI. In the subgroups of patients with other lesions, responses to the Mismatch condition were more or equally affected as in the other two conditions. This could suggest an effect of temporal or hippocampal lesions on the incidence of Mismatch abnormalities in the other subgroups of patients. Second, there was a greater incidence of Mismatch abnormalities present in the subgroup with left sided lesions that were not hippocampal sclerosis and the subgroup with left hippocampal lesions as compared with the other groups (although not significantly so). The subgroup with left-sided lesions that were not hippocampal sclerosis included 11 patients with temporal lesions. The presence of additional parietal or temporal lobe lesions in 14 patients from the subgroup with left hippocampal sclerosis could also explain the increase in the abnormalities seen. It is plausible therefore to suggest an aggravating effect of the left hemisphere lesions on the number of Mismatch abnormalities seen with long-standing temporal lobe epilepsy.

A previous study of patients with hippocampal vascular lesions showed no effect on the mismatch negativity, while patients with temporo-parietal lesions showed reduced mismatch negativity amplitude over the ipsilateral hemisphere (Alain et al, 1998). None of the patients of that study had a chronic pathological process. Our own previous clinical studies with similar sound stimuli in multiple sclerosis patients showed a variety of abnormalities for the same stimulus conditions in individual patients. In the inter-group comparison no significant differences were seen for the Onset and Frequency Change components between normal controls and multiple sclerosis patients. However, in the multiple sclerosis group, a significantly delayed MP2 was seen for stimuli in either ear, while MN1 showed significant latency delay for the right ear only (Jones et al, 2002). In another study of post-comatose patients the Mismatch response was apparently more delayed in head injury patients than were Frequency Change responses (Jones et al, 2000, b). It is possible that the Mismatch responses, while reflecting temporal processing of sound, are more sensitive to diffuse demyelination and to delays in the neuronal transmission secondary to use of anti-epileptic drugs or epileptic seizures, than to the localised lesions.

The choice of the control group subjects was made with a practical objective-proximity, easy contact, and similar age group as the patients. The normal control group was made up of technicians, research fellows and registrars of the department of Clinical

Neurophysiology, with an average education level higher than the mean education of the patients. This could possibly introduce a bias in the pre-surgical responses although there are no reports that education has any effect on evoked potentials of this latency. The mean Intelligence Quotient (I.Q.) of the patients (assumed from the surgical sample, which underwent neuropsychological evaluation) was also possibly lower than that of the normal control group (although this was not tested) and might also be affected by the disease, medication and epileptic discharges. Musical training was similar between the majority of the normal subjects and the patients (with the exception of two normal subjects with a high performance in music and three patients who also played an instrument) and probably did not play a role in the observed differences. In order to minimise the effect of reduced arousal due to drowsiness, a constant surveillance of the normal control group and the patients during recording was performed, particularly since it is known that most antiepileptic drugs do interfere with arousal. No studies relating the MMN waveform to I.Q. have apparently been published, but increases in the MMN response are seen with training and learning of the auditory standard-deviant difference (rev. Näätänen and Alho, 1995). A larger MMN response is related with an increase in the auditory discriminative capacity- obtained namely with learning of foreign languages and/or with musical training, that could be less available to the patient population than to the normal control group. It must be noted, however, that the differences observed between the normal control group and the patient subgroups were mainly in the latency of the components and not in their amplitude.

4.3 – *Are cortical auditory evoked potentials affected by surgery for temporal lobe epilepsy?*

Following surgery the MN1 component was significantly increased in amplitude ipsilaterally to the side of the surgical lesion in the right hippocampal sclerosis subgroup, when compared with the pre-surgical values. This was reflected in a lower incidence of Mismatch abnormalities on the right side after surgery, although the overall incidence of abnormalities was increased due to an increase in left-sided amplitude abnormalities. In the left hippocampal sclerosis subgroup and the subgroup with non-hippocampal sclerosis lesions no statistically significant effects of surgery were observed. This picture suggests again a bi-hemispheric effect of the surgical procedure on the incidence of abnormalities,

with ipsilateral improvement and contralateral worsening and also with a greater effect of right-sided surgery. The absence of a significant effect on MN1/MP2 latency in spite of the clinical improvement of the patients, suggests that the latency abnormalities present in the pre- and post-surgical subgroups may not be only related to the presence of seizures.

Although in certain circumstances the right hemisphere may show a preference for "musical" sound analysis (pitch discrimination, missing fundamental detection,etc- eg: Zatorre 1998, Johnsrude et al, 2000), symmetrical hemisphere activation by these complex tone stimuli is suggested by the auditory evoked potentials distribution in the normal control group and in the patients' subgroups. A surgical procedure involving the temporal lobe might disrupt the generators, producing disturbances of symmetry, and might also disrupt the interaction between the hemispheres in the treatment of sound. Bilateral effects on the amplitude of the N1 potential produced by a unilateral temporal lobe lesion have been reported (Knight et al, 1988). These authors suggested the possibility of impairment of a subcortical generator affecting both lateral expressions of N1, by loss of a facilitatory effect of the superior temporal cortex. More recently, Herrmann and Knight (2001) suggested a loss of modulatory influences from the lesioned side as a potential cause for bilateral manifestations of unilateral lesions. It is therefore possible to postulate an influence from the contralateral anterior temporal cortex, or the limbic structures, on both right and left expressions of MN1, although why a lesion should apparently have the opposite effect on the two sides is unclear.

The role of the hippocampus in the generation of the mismatch negativity is not certain. Alain et al. (1998) showed no effect of hippocampal vascular lesions on the MMN, while temporo-parietal vascular lesions caused decreased MMN amplitude only when the stimulus was given to the ear contralateral to the lesion. In animal studies, Csèpe and collaborators (reviewed by Alho, 1995) showed a very early response of the hippocampus in cats (20 ms) with the oddball paradigm which they believed to be equivalent to the MMN. On the other hand, Kropotov et al (1995), using intracerebral recordings in humans, did not detect any activity of the hippocampus in the generation of MMN. More recently, intracerebral studies detected a positivity in the hippocampus following the MMN. This positivity was assumed to be the P3a (Kropotov et al, 2000), perhaps equivalent to the MP2 of the present study. The MN1 appears to represent a temporal processing of sound, evaluating the pattern changes and relating them to a previous memory of several seconds. If the response obtained by Csèpe and collaborators is a mismatch negativity, the

hippocampus could be involved in the generation of the mismatch response as a sub-cortical source, or a factor modulating the cortical response. In this case, a hippocampal sclerosis might produce abnormalities of the component as seen in the pre-surgical group.

Some supportive evidence for an influence of the hippocampus on the MN1/MP2 comes from the results of the non-hippocampal sclerosis subgroup after surgery. In this subgroup, the surgical resection was mainly cortical with no hippocampal resection, and no post-surgical effects were seen in the amplitude or latency of the Mismatch components, although a clinical improvement was seen. Of course, one possible reason is the small number of patients, not sufficient to ensure a statistically significant result. By comparison, the significant post-surgical changes seen in the hippocampal sclerosis subgroups, along with a similar improvement in post-surgical clinical seizures, suggests a possible role of the hippocampus in the changes observed in the evoked potential parameters. A chronically damaged hippocampus might influence the occurrence of evoked potential abnormalities in the pre-surgical group, but this could be balanced by the influence of the normal hippocampus, while the removal of the lesioned hippocampus in the post-surgical groups could contribute to the significant changes in latency (reduction) and in amplitude (increase) observed in some waveforms.

Bougeard and Fischer (2002) compared hippocampal sclerosis patients after surgery with a normal control group: they found no surgical difference in the small amplitude and delayed latency observed for the N100 and P200 components in the hippocampal sclerosis patients as compared with the normal controls. This comparison was not performed in the patients of the present study. When comparing the pre- and post-surgical responses in the patients group, Bougeard and Fischer (2002) found increased post-surgical N1 amplitude ipsilaterally to the surgical excision, which they attributed to the craniotomy. These authors concluded that the damaged hippocampus, the amygdala and the temporal pole, excised during the surgical procedure, caused the abnormalities seen both pre- and post-surgically in the hippocampal sclerosis patients and proposed an activating influence of these structures on sound processing.

Apart from the volume effect of surgery on the brain tissue (meaning removal of tissue which might contribute to the auditory evoked potentials or cause a shift in the position of the generator), a positive effect of surgery which might indirectly have caused the auditory evoked potential changes was a reduction of the number of clinical seizures. Most patients at the time of the second recording presented with no seizures. If, as

considered in the pre-surgical section, seizures are a major cause of auditory evoked potential abnormalities, particularly causing latency prolongation, the elimination of clinical seizures might naturally shorten the latency of the components bilaterally. This effect might not be significantly seen in the non-hippocampal sclerosis subgroup due to its small number of subjects. However, it may be responsible for the significant bilateral shortening of latency for ON1 in both the right hippocampal sclerosis and the left hippocampal sclerosis subgroups. However, the pre-surgical assessment of these patients suggested a delay in OP2 in both subgroups and a delay in ON1 in the right hippocampal sclerosis subgroup. The bilateral latency improvement recorded after surgery could be related to the improvement in seizure control. In the non-hippocampal sclerosis subgroup the surgical procedure did not produce any effect on ON1/OP2 latency, although these patients also experienced an improvement in seizures. However, the number of patients was smaller in this group than in the other two groups, and this might contribute to the non-apparent effect of surgery. In spite of all this, it is possible that the specific structures removed in the hippocampal sclerosis subgroups may be important in the generation and /or modulation of evoked auditory potentials in patients with hippocampal sclerosis.

In the right hippocampal sclerosis subgroup there was a significant ipsilateral increase in amplitude and a possible contralateral reduction in amplitude for OP2 and CN1 after surgery. It has been suggested that CN1/CP2 origin may be within or adjacent to the primary auditory cortex (see Jones and Perez, 2001), whose tonotopically organised neurons are particularly responsive to changes of frequency (eg: Bieser 1998, Steinschneider et al., 1998; Rauschecker et al., 1995; Kaas and Hackett, 1998). The CN1 component is usually maximal at the vertex, suggesting a more posterior location of its generators as compared with the MN1, whose scalp distribution is more anterior. The relative absence of post-surgical changes in the CN1 component might reflect this anatomical difference.

The surgical procedure employed for both hippocampal sclerosis subgroups involved the resection of 3.5-4 cm of the uncus and a similar resection of the hippocampus and the amygdala. This would not directly affect the primary auditory regions located in the posterior-medial part of Heschl's gyrus, but could affect the auditory association cortex located anteriorly to Heschl's gyrus, namely on the planum polare as defined by Clarke and Rivier (1998). Knowing from the normal control group that the MN1 potential had a more anterior distribution, one might expect that this type of surgery would affect the MN1/MP2

response more than ON1/OP2 and CN1/CP2. However surgery affected several waveforms: after surgery there was increased amplitude at the ipsilateral electrodes for OP2 in the right hippocampal sclerosis subgroup, with a similar, although non-significant, effect for OP2 in the left hippocampal sclerosis subgroup. MN1 amplitude increased on the surgical side in the right hippocampal sclerosis subgroup, but no surgical effect was seen in the left hippocampal sclerosis subgroup. No changes were seen for Frequency Change responses. It is implausible that the surgical resection of some structures responsible for the ON1/OP2 could have resulted in an increase in their amplitude. Again, the improvement of seizures can better explain the improvement in amplitude of the components. Another possible explanation for the ipsilateral amplitude improvement might be the effects of the resulting skull defect on scalp recorded potentials. It is reasonable to suppose that this defect, present in all surgical patients, might induce changes in current flow that could affect the scalp field of the evoked potentials recorded. However, the contralateral amplitude reduction suggests a bilateral effect of the unilateral surgical procedure, which does not seem to be explicable in terms of skull defect.

4.4 –*How can we interpret the relationship between post-surgical changes in auditory evoked potentials and neuropsychological test scores?*

Serial changes in ON1 amplitude at right-sided electrodes correlated positively with the serial changes in performance of a Figure task in all the patients and, when studied separately, in the right hippocampal sclerosis patients subgroup, that is to say that both measures tended to vary together in the same direction. Other correlations were present in the right hippocampal sclerosis patients, but the exclusion of an outlier value made them non-significant. No significant correlation effects were seen in the left hippocampal sclerosis subgroup.

There is a recognised relationship between changes in tests of visuo-spatial memory and right mesial temporal surgery. Hermann et al (1995), using the Warrington Recognition Memory Test (Warrington, 1994), reported deficits in face recognition memory after right temporal lobectomy. Chelune and Loken (1999) reviewed the literature on right hemisphere tests and described milder deficits in memory for complex visuo-spatial material after temporal lobectomy in the right hemisphere. They stressed the right hemisphere dealing with the processing of unfamiliar and verbally uninterpretable notions as an explanation to

the difficulty in finding appropriate tasks to stimulate it. Owing for these uncertainties, the correlation between neuropsychological tests and right temporal surgical lesions has to be careful. Also, the use of mean values of the neuropsychological sub-tests was necessary in order to avoid a very large number of correlations and thus an unacceptable likelihood of Type I error. However, this would obviously reduce the specificity of the results. For the same reason, a very conservative level of significance was used in the correlation tests.

The positive correlation between the post-surgical changes of right hemisphere tasks (Figure) and right-sided evoked potentials (ON1 amplitude) suggests a similar effect of surgery on both the waveforms and the mean psychological scores. Näätanen and Picton (1987) suggested that the N1 waveform (component 1) may reflect the formation of a sensory memory trace for the eliciting stimulus. The Figure Recall test assesses the immediate registration of visual information and retention over time of a complex two dimensional figure. If the mean psychological scores are a reflection of visuo-spatial working memory, we might infer that ON1 amplitude could represent a process involving similar mechanisms and/or sharing a common anatomical substrate with visuo-spatial working memory. Such a process might be the pre-attentive auditory sensory store known as the echoic memory. This would be in accordance with the hypothesis of Bougeard and Fischer (2002), giving an important role to the hippocampus and amygdala in the auditory processing of sound.

It is important to remember the possibility that this finding may be only a statistical type I occurrence, and to support that is the absence of statistical correlations between Figure scores and other waveforms. On the other hand, the use of a highly conservative p value ($p<0.005$) may have introduced a type II error. It would have been useful to evaluate the same correlations in a larger group of patients, in order to verify these correlations, and others that were significant for a less conservative p value ($p<0.05$).

There was no significant correlation between the volume of surgical resection and changes in evoked potentials after surgery. Zatorre and colleagues described impairment of pitch discrimination, memory retention and detection of direction of pitch change in patients with right temporal lobectomies, depending on the amount of Heschl's gyrus resected (Zatorre and Samson, 1991, et al, 1994). In the present study, the absence of correlation between resection volume and auditory evoked potential changes suggests either that an insufficient volume was resected to affect the auditory responses or that the resected tissue was not functionally important for the auditory evoked potentials. Resections of the

hippocampal sclerosis subgroups were mostly of the mesial neocortex and the anterior part of the temporal pole, probably affecting the anterior secondary auditory cortex but not Heschl's gyrus. All the auditory evoked potential waveforms may be the product of generators distributed over a wide area of the cortex, needing bilateral lesions of a certain extent to be significantly affected.

Unilateral temporal lobectomy patients, although sometimes impaired in complex musical tasks like musical memory and discrimination (Liegeois-Chauvel et al, 1998; Samson and Zatorre, 1994) do not usually appear to suffer from auditory difficulties after surgery. In spite of the large number of auditory evoked potential abnormalities, only three patients reported auditory problems post-surgically, being unable to cope with the different sound sources in a "cocktail party" situation, the effect becoming progressively less severe with time. Also in common, the three patients had abnormalities of inter-hemisphere differences in auditory evoked potential latencies, suggesting that sound streaming might be affected by the delay of one hemisphere over the other. This, however, must remain entirely speculative.

4.5 -General surgical effects

When comparing the number of auditory evoked potential abnormalities before and after surgery, a mixed picture emerged with some normal components becoming abnormal while some abnormal components became normal. While few patients showed an overall improvement or worsening of the waveforms, the majority presented a mixed picture after surgery, often suggesting improvement on one side and worsening of the potentials on the other. Cranford et al (1996), analysing the P300 responses in children who had undergone temporal lobectomies and in whom seizures were reduced after surgery, found a similar picture. In the present study, while most of the patients reported a clear improvement in seizure control, it seems that central auditory processing often remained compromised, due either to the non-specific effects of long term epilepsy or to the specific dysfunction of important structures, particularly the hippocampus. The former is the most likely explanation considering the similar post-surgical findings in patients with hippocampal sclerosis and non-hippocampal sclerosis lesions. The role of the hippocampus in this picture is not clear and further studies in patients with other hippocampal conditions could

help in clarifying its importance for the generation or modulation of pre-attentive long latency auditory evoked potentials.

4.6 -Future work with long latency auditory evoked potentials related to complex tones

One of the difficulties observed with the present study was the large number of potential causes for abnormalities present in the pre-surgical patients subgroups. A possible way to elucidate this and to highlight the lesional effect could have been to have a control group with idiopathic generalised non-controlled epilepsy, with a similar use of anti-epileptic drugs, and to compare the nature and distribution of waveform abnormalities between the hippocampal sclerosis subgroup and the latter one. Another option would be to have a group of subjects with epilepsy and with no hippocampal lesions or with a more homogenic type of brain lesions producing epilepsy, in order to have a positive control. The evaluation of patient groups with different types of epilepsy (namely primary generalised epilepsy, controlled or not), and using different types of anti-epileptic drugs, could shed some light on the adverse effects suffered by these patients and which are reflected in the abnormalities seen in the auditory response to complex tones.

Twenty seven years after the discovery of the MMN (Näätänen et al, 1978) the clinical application of this waveform is still difficult due to its intraindividual variation, its interindividual variation and its small signal to noise ratio, plus necessitating long periods of recording. The MN1/MP2 responses, sharing similarities with the MMN already described, but with a much better signal to noise ratio and needing less time to acquire it, could be used in the same clinical settings already tested with the MMN, potentially resulting in better cooperation from the patient and a better elucidation of the response. This would be helpful in patients with neurological degenerative conditions that tend to cause reduced cooperation, already tested with the MMN, namely demented parkinsonian patients and patients with Alzheimer's disease. In the latter condition Pekkonen et al (1994) and Pekkonen, (2000) reported an attenuated MMN with an ISI of 1 second, suggesting that in the process of dementia the duration of the echoic memory trace becomes shorter. Also, a better elucidation of the possible relation between Neuropsychological tests and MN1

responses highlighted in the present work could improve the neuroreabilitation programs for these and other patients suffering from acute or chronic lesions of the nervous system.

In order to elucidate the relationship between the short auditory store (echoic memory), working memory and these evoked responses, a repeated study might be performed applying these stimuli to a population with well defined neuropsychological deficits.

Another possible application for the use of complex tones and auditory evoked potentials might consist in the investigation and rehabilitation of patients with central auditory processing deficits or auditory agnosias, acquired after temporal lobe lesions, or in children with linguistic impairments due to hearing difficulties. Their training could be accompanied by their neurophysiological evaluation, as a consistent and objective measure of improvement/non-improvement.

The larger signal to noise ratio of MN1 response, the non-attentive recording conditions, and the possible correlation with neuropsychological tests suggest the possibility of a wider application of the MN1 component and a possible integration of these long-latency evoked responses in clinical settings, as a measure of improvement/ deterioration of specific clinical disorders. Due to the importance of neuroreabilitation in patients with neurological disorders, the objective measurement of its achievement is of great importance.

Bibliography

Aaltonen O., Tuomainen J., Laine M., Niemi P. Cortical differences in tonal versus vowel processing as revealed by an event related potential component called mismatch negativity (MMN). Brain and Language1993; 44 (2): 139-152.

Aarts J., Binnie C., Smith A., Wilkins A. Selective cognitive impairment during focal and generalised epileptiform EEG activity. Brain 1984; 107: 293-308.

Akaho R. The effects of anti-epileptic drugs on cognition on normal volunteers. Psychiatry and Clinical Neurosciences 1996; 50: 61-69.

Alain C., Woods D.L., Knight R.T. A distributed cortical network for auditory sensory memory in humans. Brain Research 1998; 812 (1-2): 23-37.

Alain C., Achim A., Woods D.L. Separate memory-related processing for auditory frequency and patterns. Psychophysiology 1999; 36 (6): 737-744.

Aldenkamp A.P. Effects of anti-epileptic drugs on cognition. Epilepsia 2001; 42: 46-49.

Alho K. Cerebral generators of mismatch negativity (MMN) and its magnetic counterpart (MMNm) elicited by sound changes. Ear and Hearing 1995; 16 (1): 38-51.

Alho K., Tervaniemi M., Huotilainen M., Lavikainen J., Tiitinen H., Ilmoniemi R.J., Knuutila J., Näätänen R. Processing of complex sounds in the human auditory cortex as revealed by magnetic brain responses. Psychophysiology 1996; 33 (4): 369-375.

Alho K., Woods D.L., Algazi A., Knight R.T., Näätanen R. Lesions of frontal cortex diminish the auditory mismatch negativity. Electroencephalography and clinical Neurophysiology, 1994; 91: 353-362.

Arlinger S., Elberling C., Bak C., Kofoed B., Lebech J., Saermark K. Cortical magnetic fields evoked by frequency glides of a continuous tone. Electroencephalography and clinical Neurophysiology, 1982; 54: 642-653.

Barr W.B. Examining the right temporal lobe's role in non-verbal memory. Brain and Cognition, 1997; 35: 26-41.

Baxendale S. The hippocampus: functional and structural correlations. Seizure 1995; 4 (2): 105-117.

Baxendale S. The role of functional MRI in the pre-surgical investigation of temporal lobe epilepsy patients: a clinical perspective and review. Journal of Clinical and Experimental Neuropsychology 2002; 24: 664-676.

Baxendale S., Thompson P., Kitchen N. Post-operative hippocampal remnants shrinkage and memory decline: a dynamic process. Neurology 2000; 55: 243-249.

Baxendale S.B. The role of the hippocampus in recognition memory. Neuropsychologia 1997; 35: 591-598.

Baxendale S.B., Thompson P.J., Paesschen W.v. A test of spatial memory and its clinical utility in the pre-surgical investigation of temporal lobe epilepsy patients. Neuropsychologia 1998; 36 (7): 591-602.

Bergin P., Thompson P., Baxendale S., Fish D., Shorvon S. Remote memory in epilepsy. Epilepsia 2002; 41: 231-239.

Berkovic S., McIntosh A., Kalnins R., Jackson G.D., Fabinyi G.C., Brasenor G.A., Bladin P.F., Hopper J.L. Pre-operative MRI predicts outcome of temporal lobectomy: an actuarial analysis. Neurology 1995; 45: 1358-1363.

Bieser A. Processing of twitter call fundamental frequencies in insula and auditory cortex of squirrel monkeys. Experimental Brain Research 1998; 122: 139-148.

Bieser A., Muller Preuss P. Auditory responsive cortex in the squirrel monkey: neural responses to amplitude modulated sounds. Experimental Brain Research 1996; 108: 273-284.

Bougeard R., Fischer C. The role of the temporal pole in auditory processing. Epileptic Disorders. Vol. 4, Supplement 1, 2002: 29-32

Bregman A.S. Summary and conclusions: what we do and do not know about auditory scene analysis. In: Auditory scene analysis. M.I.T. Press 1994. 641-705.

Britt R., Starr A. Synaptic events and discharge patterns of cochlear nucleus cells.II. Frequency modulated tones. Journal of Neurophysiology 1976; 39: 179-194.

Brugge J.F., Reale R.A. Auditory cortex. In: Cerebral cortex. Association and auditory cortices. A.Peters and E.G.Jones, editor. Plenum, 1985: 229-267.

Caravaglios G., Natale E., Ferraro G., Fierro B., Raspanti G., Danielie O. Auditory event-related potentials (P300) in epileptic patients. Neurophysiologie Clinique 2001; 31: 121-129.

Chatrian G.E., Petersen, M.C., Lazarte, J.A. Responses to clicks from the human brain: some depth electrographic observations. Electroencephalography and clinical Neurophysiology 1960; 12: 479-488.

Chelune G.J., Loken W. Mesial temporal sclerosis and memory functions. In: The epilepsies: aetiologies and prevention. Academic Press. 1999: 215-225.

Clarke S., Bellman A., Meuli R.A., Assal G., Steck A. Auditory agnosia and auditory spatial deficits following left hemispheric lesions: evidence for distinct processing pathways. Neuropsychologia 2000; 38: 797-807.

Clarke S., Rivier F. Compartments within human primary auditory cortex: evidence from cytochrome oxidase and acetilcolinestherase staining. The European Journal of Neuroscience 1998; 10: 741-745.

Clusmann H., Schramm J., Kral T., Helmstaedter C., Ostertun B., Fimmers R., Haun D., Elger C.E. Prognostic factors and outcome after different types of resection for temporal lobe epilepsy. Journal of Neurosurgery 2002; 97: 1131-1141.

Cohen Y.E. Maps versus clusters: different representations of auditory space in the midbrain and the forebrain. Trends in Neurosciences 1999; 22: 128-135.

Coles M.G.H., Rugg M.D. Event related brain potentials: an introduction. In Electrophysiology of mind: event related brain potentials and cognition. Michael D. Rugg and Michael G. H. Coles, editors. Oxford Psychology Series, 25. Oxford University Press, 1995.1-23

Connolly J.F. The influence of stimulus intensity, contralateral masking and handedness on the temporal N1 and the T-complex components of the auditory N1 wave. Electroencephalography and clinical Neurophysiology 1993; 86: 58-68.

Coughlan A., Hollows S.E. Adult Memory and Information Processing Battery. Leeds, UK: Psychological Department, St James Hospital, 1985.

Cowan N. On short and long auditory stores. Psychological Bulletin 1984; 96: 341-370.

Cowan N., Winkler I., Teder W., Näätanen R. Memory prerequisites of mismatch negativity in the auditory event-related potential (ERP). Journal of Experimental Psychology. Learning, Memory and Cognition 1993; 19: 909-921.

Cranford J.L., Kennalley T., Svoboda W., Hipp K. Changes in central auditory processing following temporal lobectomies in children. Journal of the American Academy of Audiology 1996; 7(4):289-295.

Creutzfeldt O. Functional topography of sensory and motor areas. Cortex Cerebri: performance, structural and functional organization of the cortex. Oxford University Press, 1995: 221-369.

Creutzfeldt O., Ojemann G., Lettich E. a). Neuronal activity in the human lateral temporal lobe. I. Responses to speech. Experimental Brain Research 1989; 77: 451-475.

Creutzfeldt O., Ojemann G., Lettich E. b). Neuronal activity in the human lateral temporal lobe. II. Responses to the subject own voice. Experimental Brain Research 1989; 77: 476-489.

Creutzfeldt O., Ojemann G. Neuronal activity in the human lateral temporal lobe. III. Activity changes during music. Experimental Brain Research 1989; 77: 490-498.

de Charms R.C., Blake D.T., Merzenich M.M. Optimizing sound features for cortical neurons. Science 1998; 280: 1439-1443.

Deouell L.Y., Bentin S., Soroker N. Electrophysiological evidence for an early (pre-attentive) information processing deficit in patients with right hemisphere damage and unilateral neglect. Brain 2000; 123: 353-365.

Dodrill C., Willenski A. Neuropsychological abilities before and after 5 years of stable antiepileptic drug therapy. Epilepsia 1992; 33: 327-334.

Drake M.E. Jr., Burgess R.J., Gelety T.J., Ford C.E., Brown M.E. Long-latency auditory event-related potentials in epilepsy. Clinical Electroencephalography 1986; 17: 10-13.

Drake M.E. Jr., Pakalnis A., Padamadan H., Hietter S.A., Brown M. Effect of anti-epileptic drug monotherapy and polypharmacy on visual and auditory evoked potentials. Electromyography and clinical Neurophysiology 1989; 29: 55-58.

Duncan J.S. Temporal lobe epilepsy. In: Epilepsy 2000: from science to patient. J.S.Duncan, S.J.M.Sisodyia, J.E.Small, editors. 2000: 133-135.

Dupont S., Samson Y., Le Bihan D., Baulac M. Anatomy of verbal memory: a functional MRI study. Surgical and Radiological Anatomy 2002; 24: 57-63.

Dupont S., Samson Y., Van de Moortele P.F., Samson S., Poline J.B., Hasboun D., Le Bihan D., Baulac M. b) Bilateral hemispheric alteration of memory processes in right medial temporal lobe epilepsy. Journal of Neurology, Neurosurgery and Psychiatry 2002; 73: 478-485.

Engel J., Williamson P., Wieser H.-G. Mesial temporal lobe epilepsy. In: Epilepsy: a compreensive textbook. J.Engel Jr, T.A. Pedley, editors. Lipincott Raven, 1997: 2417-2426.

Engelien A., Schulz M., Ross B., Arolt V., Pantev C. A combined functional in vivo measure for primary and secondary auditory cortices. Hearing Research 2000; 148: 153-160.

Falconer M.A. Genetic and related aetiological factors in temporal lobe epilepsy: a review. Epilepsia 1971; 12: 13-31.

Fischer C., Morlet D., Bouchet P., Luaute J., Jourdan C., Salord F. Mismatch negativity and late auditory evoked potentials in comatose patients. Clinical Neurophysiology 1999; 110 (9): 1601-1610.

Fitzpatrick D.C., Batra R., Stanford T.R., Kuwada S. A neuronal population code for sound localization. Nature 1997; 388: 871-874.

Ford G.M., Mathalon D.H., Kalba S., Marsh L.P.A. N1 and P300 abnormalities in patients with schizophrenia, epilepsy and epilepsy with schizophrenia like features. Biological Psychiatry 2001; 49: 848-860.

Fukai M., Motomura N., Kobayashi S., Asaba H., Sakai T. Event-related potentials (P300) in epilepsy. Acta neurolologica Scandinavia 1990; 82: 197-202.

Giard M.H., Perrin F., Pernier J., Bouchet P. Brain generators implicated in the processing of auditory stimulus deviance: a topographic event-related potential study. Psychophysiology 1990; 27 (6): 627-640.

Goblick T., Pfeiffer R.R. Time domain measurements of cochlear nonlinearities using combination click stimuli. Journal of the Acoustical Society of America 1969; 46: 924-938.

Godey B., Schwartz D., de Graaf J.B., Chauvel P., Liegois-Chauvel C. Neuromagnetic source localization of auditory evoked fields and intracerebral evoked potentials: a comparison of data in the same patients. Clinical Neurophysiology 2001; 112: 1850-1859.

Greenwood D.D., Goldberg J.M. Response of neurons in the cochlear nuclei to variations in noise bandwidths and to tone noise combinations. Journal of the Acoustical Society of America 1970; 47: 1022-1040.

Griffiths T.D. Human complex sound analysis. Clinical Science (London) 1999; 96 (3): 231-234.

Gulick W.L., Gescheider A.G., Frisina D.R. a) Structure and neural projections of the internal ear. In: Hearing: physiological accoustics, neural coding and psychoaccoustics. Oxford University Press, 1989: 91-114.

Gulick W.L., Gescheider A.G., Frisina D.R. Central auditory system. In: Hearing: physiological accoustics, neural coding and psychoaccoustics. Oxford University Press, 1989: 188-216.

Hackett T.A., Stepniewska I., Kaas J.H. Subdivisions of auditory cortex and ipsilateral cortical connections of the parabelt auditory cortex in macaque monkeys. Journal of Comparative Neurology 1998; 394: 475-495.

Hari R, Pelizzone M, Makëla JP, Hallstrom J, Leinonen L, Lounasmaa OV. Neuromagnetic responses of the human auditory cortex to on and offsets of noise bursts. Audiology 1987; 26: 31-43.

Hari R., Hamaläinen M., Ilmoniemi R.J. et al. Responses of primary auditory cortex to pitch changes in a sequence of tone pips: neuromagnetic recordings in man. Neuroscience Letters 1984; 50: 127-132.

Hermann B., Seidenberg M., Schoenfeld J., Davies K. Neuropsychological characteristics of the syndrome of mesial temporal lobe epilepsy. Archives of Neurology 1997; 54: 369-376.

Hermann B., Connell B., Barr W.B., Wyler A.R. a) The utility of the Warrington Recognition Memory Test for temporal lobe epilepsy: pre- and post-operative studies. Journal of Epilepsy 1995; 8: 139-145.

Hermann B., Seidenberg M., Haltiner A., Wyler A.R. b) Relationship of age of onset, chronologic age and adequacy of preoperative performance to verbal memory change after anterior temporal lobectomy. Epilepsia, 1995; 36 (2): 137-145.

Herrmann C.S., Knight R.T. Mechanisms of human attention: event-related potentials and oscillations. Neuroscience and Biobehavioral Reviews 2001; 25(6): 465-476.

Holmes G., Dodrill C.B., Ojemann G., Wilenski A.J., Ojeman L. Outcome following surgery in patients with bitemporal interictal epileptiform patterns. Neurology 1997; 48: 1037-1040.

Howard M.A., III, Volkov I.O., Abbas P.J., Damasio H., Ollendieck M.C., Granner M.A. A chronic microelectrode investigation of the tonotopic organization of human auditory cortex. Brain Research 1996; 724: 260-264.

Howard M.A., Volkov I.O., Mirsky R., Garell P.C., Noh M.D., Granner M., Damasio H., Steinschneider M., Reale R.A., Hind J.E., Brugge J.F. Auditory cortex on the human posterior superior temporal gyrus. Journal of Comparative Neurology 2000; 416: 79-92.

Hung J., Jones S.J., Vaz Pato M. Scalp potentials to pitch change in rapid tone sequences: a correlate of sequential stream segregation. Experimental Brain Research 2001; 140(1):56-65.

Ilvonen T.M., Kujala T., Tervaniemi M., Salönen O., Näätänen R., Pekkönen E. The processing of sound duration after left hemisphere stroke: event-related potential and behavioral evidence. Psychophysiology 2001; 38: 622-628.

Imada T., Hari R., Loveless N.E., McEvoy L., Sams M. Determinants of the auditory mismatch. Electroencephalography and clinical Neurophysiology, 1993; 87: 144-153.

Johnson R. Auditory and visual P300 in temporal lobectomy patients: evidence for modality dependence generators. Psychophysiology 1989; 26: 633-650.

Johnsrude I., Penhune V., Zatorre R.J. Functional specificity in the right human auditory cortex for perceiving pitch direction. Brain 2000; 123: 155-163.

Jones S.J. Divisions of the auditory cortex suggested by EPs to synthesised instrumental tones. Electroencephalography and clinical Neurophysiology, 1999; Suppl 49: 41-46.

Jones S.J. Memory-dependent auditory evoked potentials to change in the binaural interaction of noise signals. Electroencephalography and clinical Neurophysiology 1991; 80: 399-405.

Jones S.J., Byrne C. The AEP T-complex to synthesised musical tones: left-right asymmetry in relation to handedness and hemisphere dominance. Electroencephalography and clinical Neurophysiology 1998; 108: 355-360.

Jones S.J., Longe O., Vaz Pato M. Auditory evoked potentials to abrupt pitch and timbre change of complex tones: electrophysiological evidence of "streaming"? Electroencephalography and clinical Neurophysiology 1998; 108: 131-142.

Jones S.J., Perez N. The auditory 'C-process': analyzing the spectral envelope of complex sounds. Clinical Neurophysiology 2001;112(6): 965-975.

Jones S.J., Sprague L., Vaz Pato M. Electrophysiological evidence for a defect in the processing of temporal sound patterns in multiple sclerosis. Journal of Neurology, Neurosurgery and Psychiatry 2002; 73: 561-567.

Jones S.J., Vaz Pato M., Sprague L.a) Spectro-temporal analysis of complex tones: two cortical processes dependent on retention of sounds in the long auditory store. Clinical Neurophysiology 2000; 111: 1569-1576.

Jones S.J., Vaz Pato M., Sprague L., Stokes M., Munday R., Haque N.b) Auditory evoked potentials to spectro-temporal modulation of complex tones in normal subjects and patients with severe brain injury. Brain 2000; 123: 1007-1016.

Kaas J.H., Hackett T.A. Subdivisions of the auditory cortex and levels of processing in primates. Audiology and.Neuro-otology 1998; 3: 73-85.

Kane N.M., Curry S.H., Rowlands C.A., Manara A.R., Lewis T., Moss T., Cummings B.H., Butler S.R. Event related potentials- neurophysiological tools for predicting emergence and early outcome from traumatic coma. Intensive Care Medicine 1996; 22: 39-46.

Kaukoranta E., Sams M., Hari R., Hamaläinen M, Näätänen R. Reactions of human auditory cortex to a change in tone duration. Hearing Research 1989; 41: 15-21.

Kelly J.B., Whitfield I.C. Effects of auditory cortical lesions in discrimination of raising and falling frequency modulated tones. Journal of Neurophysiology. 1971; 34: 803-816.

Kelly J.P. Hearing. In: Principles of neural science. Eric R.Kandel, James H.Schwartz, Thomas M.Jessel, editors. Prentice Hall International Inc., 1991: 467-499.

Khanna S.M., Tonndorf J. Tympanic membrane vibration in cats studied by time averaged holography. Journal of the Acoustical Society of America 1972; 51: 1904-1920.

King A.J., Schnupp J.W.H. Visualizing the auditory cortex. Current Biology 1998; 8: R784-R787.

Knight R.T., Hillyard S.A., Woods D.L., Neville H.J. The effects of frontal and temporal-parietal lesions on the auditory evoked potential in man. Electroencephalography and clinical Neurophysiology 1980; 50: 112-124.

Knight R.T.Contribution of the human hippocampal region to novelty detection. Nature 1996; 383: 256-258.

Knight R.T., Scabini D., Woods D.L., Clayworth C. The effects of lesions of superior temporal gyrus and inferior parietal lobe on temporal and vertex components of the human auditory evoked potentials. Electroencephalography and clinical Neurophysiology 1988; 70: 499-509.

Koseoglu E., Karaman Y. Auditory event related potentials relate with the clinical progression in idiopathic generalized epilepsy. Electromyography and clinical Neurophysiology 2001; 41: 53-57.

Kraus N., McGee T. Auditory event-related potentials. In: Handbook of clinical audiology, 4th ed. Eds. Jack Katz, Wilkins & Wilkins, 1994: 406-423.

Kraus N., McGee T., Carrell T.D., Sharma A. Neurophysiologic bases of speech discrimination. Ear and Hearing. 1995; 16 (1): 19-37.

Kraus T., Kileny, P., McGee T. Middle latency auditory event-related potentials. In: Handbook of clinical audiology, 4th ed. Eds. Jack Katz, Wilkins & Wilkins, 1994: 387-405.

Kropotov J.D., Alho K., Näätänen R., Ponomarev V., Kropotova O.V., Anichkov A.D., Nechaev V.B. Human auditory cortex mechanisms of preattentive sound discrimination. Neuroscience Letters 2000; 280 (2): 87-90.

Kropotov J.D., Näätänen R., Sevostianov A.V., Alho K., Reinikäinen K., Kropotova O.V. Mismatch negativity to auditory stimulus change recorded directly from the human temporal cortex. Psychophysiology 1995; 32 (4): 418-422.

Lang A.H., Eerola O., Korpilahti P., Holopainen I., Salo S., Aältonen O. Practical issues in the clinical application of mismatch negativity. Ear and Hearing 1995; 16 (1): 118-130.

Langner G., Schreiner C.E. Periodicity coding in the inferior colliculus of the cat. I. Neuronal mechanisms. Journal of Neurophysiology 1988; 60 (6): 1799-1822.

Lee T.M.C., Yop J.T.H., Jones-Gotman M. Memory deficits after resection from left and right anterior lobe in humans. Epilepsia 2002; 43: 283-292.

Lemieux L., Barker G.J. Measurement of small inter-scan fluctuations in voxell dimensions in magnetic resonance images using registration. Medical Physics 1998; 25: 1049-1054.

Leonard C.M., Puranik C., Kuldau J.M., Lombardino L.J. Normal variation in the frequency and location of human auditory cortex landmarks. Heschl's gyrus: where is it? Cerebral Cortex 1998; 8: 397-406.

Levänen S., Ahonen A., Hari R., McEvoy L., Sams M. Deviant auditory stimuli activate human left and right auditory cortex differently. Cerebral Cortex 1996; 6: 288-296.

Levänen S., Hari R., McEvoy L., Sams M. Responses of the human auditory cortex to changes in one versus two stimulus features. Experimental.Brain Research 1993; 97: 177-183.

Li L., Dubeau F., Andermann F., Fish D.R., Watson C., Cascino G.D., Berkovic S.F., Moran N., Duncan J.S., Olivier A., Leblanc R., Harkness W. Periventricular nodular heterotopia and intractable temporal lobe epilepsy: poor outcome after temporal lobe resection. Annals of .Neurology 1997; 41: 662-668.

Liasis A., Towell A., Alho K., Boyd S. Intracranial identification of an electric frontal cortex response to auditory stimulus change: a case study. Brain Research. Cognitive Brain Research 2001; 11: 227-233.

Liasis A., Towell A., Boyd S. Intracranial auditory detection and discrimination potentials as substrates of echoic memory in children. Brain Research. Cognitive Brain Research 1999; 7: 503-506.

Liasis A., Towell A., Boyd S. Intracranial evidence for differential encoding of frequency and duration discrimination responses. Ear and Hearing 2000; 21: 252-256.

Liegeois-Chauvel C., Giraud K., Badier J.M., Marquis P., Chauvel P. Intracerebral evoked potentials in pitch perception reveal a functional assymetry of the human auditory cortex. Annals of New York Academy of Sciences 2001; 930: 117-132.

Liegeois-Chauvel C., Peretz I., Babai M., Laguitton V., Chauvel P. Contribution of different cortical areas in the temporal lobes to music processing. Brain. 1998; 121: 1817-1818.

Liegois-Chauvel C., Musolino A., Chauvel P. Localization of the primary auditory area in man. Brain 1991; 114: 139-153.

Makëla J.P., Hari R., Linnankivi A. Different analysis of frequency and amplitude modulations of a continuous tone in the human auditory cortex: a neuromagnetic study. Hearing Research 1987; 27(3): 257-264.

Makëla J.P., Salmelin R., Kotila M., Salonen O., Laaksonen R., Hokkanen L., Hari R. Modification of neuromagnetic cortical signals by thalamic infarction. Electroencephalography and clinical Neurophysiology, 1998; 106: 433-453.

Manley J.A., Muller Preuss P. Response variability of auditory cortex cells in the squirrel monkey to constant accoustic stimuli. Experimental Brain Research 1978; 32: 171-180.

Martin B.A., Boothroyd A. Cortical auditory event-related potentials in response to periodic and aperiodic stimuli with the same spectral envelope. Ear and Hearing 1999; 20: 33-44.

Mathern G., Babb T.L., Vickrey B., Melendez M., Pretorius J. Traumatic compared to non traumatic clinical pathological associations in temporal lobe epilepsy. Epilepsy Research 1994; 19: 129-139.

Mathern G., Pretorius J., Babb T.a) Influence of the type of initial precipitating injury and at what age it occurs on course and outcome in patients with temporal lobe seizures. Journal of Neurosurgery 1995; 82: 205-207.

Mathern G.W., Babb T.L., Vickrey B.G., Melendez M., Pretorius J.K.b) The clinical-pathogenic mechanisms of hippocampal neuron loss and surgical outcomes in temporal lobe epilepsy. Brain. 1995 Feb;118 (Pt 1):105-18.

McCarthy G., Wood C. Intracranial recordings of endogenous event related potentials in humans. Electroencephalography and clinical Neurophysiology 1987; 39: 331-337.

McCarthy G., Wood C.C. Scalp distribution of event-related potentials: an ambiguity associated with analysis of variance models. Electroencephalography and clinical Neurophysiology 1985; 62: 203-208.

Mervaala E., Nousiainen U., Kinnunen J., Vapalahti M., Riekkinen P. Pre- and post-operative auditory event related potentials in temporal lobe epilepsy. Epilepsia 1992; 33: 1029-1035.

Merzenich M.M, Knight P.L., Roth G.L. Representation of the cochlea within the primary auditory cortex in the cat. Journal of Neurophysiology 1975; 28: 231-249.

Merzenich M.M., Brugge J.F. Representation of the cochlear partition on the superior temporal plane of the macaque monkey. Brain Research 1973; 50: 275-296.

Middlebrooks J.C. Cortical representations of auditory space. In: The new cognitive neurosciences. Michael S.Gazzaniga, editor. MIT Press, 2000: 425-436.

Møller A.R. a). Physiology of the cochlea. In: Hearing: its physiology and pathophysiology. Academic Press, 2000: 71-95.

Møller A.R. b). Anatomy of the auditory nervous system. In: Hearing: its physiology and pathophysiology. Academic Press, 2000: 129-151.

Møller A.R. c). Representation of frequency in the auditory system. In: Hearing: its physiology and pathophysiology. Academic Press, 2000: 151-197.

Møller A.R. Coding of time varying sounds in the cochlear nucleus. Audiology 1978; 17: 446-468.

Møller A.R. d). Coding of complex sounds. In: Hearing: its physiology and pathophysiology. Academic Press, 2000; 197-241.

Moore B.C.J. The nature of sound and the structure and function of the auditory system. In: An introduction to the psychology of hearing. Academic Press.1997: 1-48.

Moran N.F., Lemieux L., Maudgil D., Kitchen N.D., Fish D.R., Shorvon S.D. Analysis of temporal lobe resections in MR images. Epilepsia 1999; 40: 1077-1084.

Mouritzen Dam A. The aetiology of mesial temporal sclerosis. In: The temporal lobes and the limbic system. M R Trimble, T G Bolwig, editors. Wrightson Biomedical Publishing, 1992: 129-136.

Näätänen R, Gaillard AW, Mantysalo S. Early selective-attention effect on evoked potential reinterpreted. Acta Psychol (Amst). 1978 Jul; 42(4):313-29.

Näätänen R. and Picton T.W. The N1 wave of the human electric and magnetic response to sound: a review and an analysis of the component structure. Psychophysiology 1987; 24 (4):375-425.

Näätänen R., Paavilainen P., Alho K., Reinikainen K., Sams M. Do event-related potentials reveal the mechanism of the auditory sensory memory in the human brain? Neuroscience Letters 1989; 98: 217-221.

Näätänen R, Lehtokoski A, Lennes M, Cheour M, Huotilainen M, Iivonen A, Vainio M, Alku P, Ilmoniemi RJ, Luuk A, Allik J, Sinkkonen J, Alho K. Language-specific phoneme representations revealed by electric and magnetic brain responses. Nature. 1997; 30; 385: 432-434.

Näätänen R., Paavilainen P., Alho K., Reinikainen K., Sams M. The mismatch negativity to intensity changes in an auditory stimulus sequence. Electroencephalogra- phy and clinical Neurophysiology, Suppl.1987; 40:125-131.

Näätänen R., Teder W., Alho K., Lavikainen J. Auditory attention and selective input modulation: a topographical ERP study. Neuroreport 1992; 3: 493-496.

Näätänen R., Alho K. Mismatch negativity- a unique measure of sensory processing in audition. The International Journal of Neurosciences 1995; 80:317-332.

Nakasato N., Kumabe T., Kanno A., Ohtomo S., Mizoi K., Yoshimoto T. Neuromagnetic evaluation of cortical auditory function in patients with temporal lobe tumours. Journal of .Neurosurgery 1997; 86: 610-618.

Nelken I., Rotman Y., Yosef O.B. Responses of auditory cortex neurons to structural features of natural sounds. Nature 1999; 397: 154-157.

Nishitani N., Ikeda A., Nagamine T., Honda M., Mikuni N., Kimura J., Shibasaki H. The role of the hippocampus in auditory processing studied by event-related electric potentials and magnetic fields in epilepsy before and after temporal lobectomy. Brain 1999; 122: 687-707.

Noda K., Tonoike M., Doi K., Koizuka I., Yamaguchi M., Hamada T., Seo R., Kubo T. A pitch glide activates an intermediate response between auditory N1 and mismatch negativity. Neuroreport 1999; 10 (9): 1909-1912.

Nordby H., Roth W.T., Pfefferbaum A. Event-related potentials to breaks in sequences of alternating pitches or interstimulus intervals. Psychophysiology 1988; 31: 544-552.

Paavilainen P., Karlsson M.L., Reinikainen K., Näätanen R. Mismatch negativity to change in spatial location of an auditory stimulus. Electroencephalography and clinical Neurophysiology, 1989; 73 (2): 129-141.

Paavilainen P., Valppu S., Näätanen R. The additivity of the auditory feature analysis in the human brain as indexed by the mismatch negativity: 1+1 approximately 2 but 1+1+1<3. Neuroscience Letters 2001; 301: 179-182.

Pantev C., Bertrand O., Eulitz C., Verkindt C., Hampson S., Schuierer G., Elbert T. Specific tonotopic organizations of different areas of the human auditory cortex revealed by simultaneous magnetic and electric recordings. Electroencephalography and clinical Neurophysiology 1995; 94: 26-40.

Pekkonen E. Mismatch negativity in aging and in Alzheimer's and Parkinson's diseases. Audiology and Neuro-otology 2000; 5: 216-224.

Penhune V.B., Zatorre R.J., MacDonald J.D., Evans A.C. Interhemispheric anatomical differences in human primary auditory cortex: probabilistic mapping and volume measurement from magnetic resonance scans. Cerebral Cortex 1996; 6: 661-672.

Perrault, N. and Picton, T.W. Event-related potentials recorded from the scalp and nasopharynx. I. N1 and P2.Electroencephalography and clinical Neurophysiology, 1984, 59:177-194.

Peronnet F., Michel F., Echallier J.F., Girod J. Coronal topography of human auditory evoked responses. Electroencephalography and clinical Neurophysiology, 1974; 37: 225-230.

Phillips D.P., Semple M.N., Calford M.B., Kitzes L.M. Level dependent representation of stimulus frequency in cat primary auditory cortex. Experimental.Brain Research 1994; 102: 210-226.

Pickles J.O. a). The outer and middle ears. In: An introduction to the psychology of hearing. Academic Press, 1982: 10-23.

Pickles J.O. b). The cochlea. In: An introduction to the psychology of hearing. Academic Press, 1982: 24-70.

Pickles J.O. c). The auditory nerve. In: An introduction to the psychology of hearing. Academic Press, 1982: 71-106.

Pickles J.O. d). The brain stem nuclei. In: An introduction to the psychology of hearing. Academic Press, 1982: 154-93.

Pickles J.O. e). The auditory cortex. In: An introduction to the psychology of hearing. Academic Press, 1982: 195-227.

Picton T.W., Alain C., Otten L., Ritter W., Achim A. Mismatch negativity : different water in the same river. Audiology and Neuro-otology 2000; 5: 111-139.

Pihko E., Leppasaari T., Lyytinen H. Brain reacts to occasional changes in duration of elements in a continuous sound. Neuroreport 1995; 6 (8): 1215-1218.

Puce A., Bladin P.F. Scalp and limbic P3 event-related potentials in the assessment of patients with temporal lobe epilepsy. Epilepsy 1989;52 (5):629-634.

Rademacher J., Caviness V.S.Jr., Steinmetz H., Galaburda A. Topographical variation of the human primary cortices; implications for neuroimaging, brain mapping and neurobiology. Cerebral Cortex 1993; 3: 313-329.

Rausch R. Epilepsy surgery within the temporal lobe and its short-term and long-term effects on memory. Current Opinion in Neurology 2002; 15: 185-189.

Rauschecker J.P., Tian B., Hauser M. Processing of complex sounds in the macaque non-primary auditory cortex. Science 1995; 268: 111-114.

Rauschecker J.P. Processing of complex sounds in the auditory cortex of cat, monkey, and man. Acta Oto-laryngologica. Suppl 1997; 532: 34-38.

Reale R.A., Imig T.J. Tonotopic organization of the auditory cortex in the cat. Journal of Comparative Neurology 1980; 192: 265-291.

Rivier F., Clarke S. Cytochrome oxidase, acetylcholinesterase, and NADPH-diaphorase staining in human supratemporal and insular cortex: evidence for multiple auditory areas. Neuroimage. 1997; 6: 288-304.

Robin D.A., Tranel D., Damasio H. Auditory perception of temporal and spectral events in patients with focal left and right cerebral lesions. Brain and Language 1990; 39: 539-555.

Saarinen J., Paavilainen P., Schröger E., Tervaniemi M., Näätanen R. Representation of abstract attributes of auditory stimuli in the human brain. Neuroreport 1992; 3 (12): 1149-1151.

Sams M., Paavilainen P., Alho K., Näätanen R. Auditory frequency discrimination and event-related potentials. Electroencephalography and clinical Neurophysiology 1985; 62 (6): 437-448.

Samson S., Zatorre R.J. Contribution of the right temporal lobe to musical timbre discrimination. Neuropsychologia 1994; 32: 231-240.

Scherg M., von Crammon D. Evoked dipole source potentials of the human auditory cortex. Electroencephalography and clinical Neurophysiology 1986; 39: 609-620.

Schreiner C.E. Spatial distribution of responses to simple and complex sounds in the primary auditory cortex. Audiology and Neuro-otology 1998; 3: 104-122.

Schreiner C.E., Urbas J.V. Representation of amplitude modulation in the auditory cortex of the cat. II. Comparison between cortical fields. Hearing Research 1988; 32: 49-63.

Schröger E. An event-related potential study of sensory representation of unfamiliar tonal patterns. Psychophysiology 1994; 31: 175-181.

Schröger E., Näätanen R., Paavilainen P. Event related potentials reveal how non- attended complex sound patterns are represented by the human brain. Neuroscience Letters 1992; 146: 183-186.

Schröger E., Tervaniemi M., Winkler I., Wolff C., Näätanen R. Processing of interaural cues used for auditory lateralization as revealed by the mismatch negativity. In: Contributions to psychological acoustics. Results of the Seventh Oldenburg Symposium on psychological acoustics. August Schick and Maria Klatte, editor. 1997.

Schröger E., Tervaniemi M., Wolff C., Näätänen R. Preattentive periodicity detection in auditory patterns as governed by time and intensity information. Brain Research. Cognitive Brain Research. 1996; 4(2):145-148.

Schröger E., Winkler I. Presentation rate and magnitude of stimulus deviance effects on human pre-attentive change detection. Neuroscience Letters 1995; 193: 185-188.

Schuppert M., Munte T., Wiering B.M., Altenmuller E. Receptive amusia: evidence for cross-hemispheric neural networks underlying music processing strategies. Brain 2000; 123: 546-559.

Semple M.N., Aitkin L.M. Representations of sound frequency and laterality by units in central nucleus of the cat inferior colliculus. Journal of.Neurophysiology 1979; 42: 1626-1639.

Shamma S.A. Physiological basis of timbre perception. In: The new cognitive neurosciences..Michael S.Gazzaniga, editor. MIT Press, 2000: 411-422.

Shamma S.A., Fleshman J.W., Wiser P.R. Organization of response areas in primary auditory cortex in the ferret; spectral organization columns. Journal of Neurophysiology. 1993; 69: 367-383.

Smith M.E., Halgren E. Dissociations of recognition memory components following temporal lobe lesions. Journal of Experimental Psychology. Learning, Memory and Cognition 1989;15 (1): 50-60.

Soysal A., Atakli D., Atay T., Altintas H., Baybas S., Arpaci B. Auditory event-related potentials (P300) in partial and generalized epileptic patients. Seizure 1999; 8: 107-110.

Steinschneider M., Reser D.H., Fishman Y.I., Schroeder C.E., Arezzo J.C. Click train encoding in primary auditory cortex of the awake monkey: evidence for two mechanisms subserving pitch perception. Journal of the Acoustical Society of America 1998; 104: 2935-2955.

Sussman E., Ritter W., Vaughan-H.G.J. An investigation of the auditory streaming effect using event-related brain potentials. Psychophysiology. 1999; 36 (1): 22-34.

Taub J.M., Tanguay P.E., Clarckson D. Electroencephalographic and reaction time assymetries to musical chord stimuli. Physiological Behaviour 1976; 17: 925-930.

Tervaniemi M., Schröger E., Näätänen R. Pre-attentive processing of spectrally complex sounds with asynchronous onsets: An event-related potential study with human subjects. Neuroscience.Letters. 1997; 227 (3): 197 -200.

Tervaniemi M., Alho K., Paavilainen P., Sams M. Absolute pitch and event-related potentials. Music Perception 1993; 10: 305-316.

Tervaniemi M., Saarinen J., Paavilainen P., Danilova N., Näätanen R. Temporal integration of auditory information in sensory memory as reflected by the mismatch negativity. Biological Psychology 1994; 38: 157-167.

Tiitinen H., Alho K., Huotilainen M., Ilmoniemi R.J., Simola J., Näätanen R. Tonotopic auditory cortex and the magnetoencephalographic (MEG) equivalent of the mismatch negativity. Psychophysiology 1993; 30: 537-540.

Trenerry M. Clinical neuropsychology in epilepsy surgery. In: Epilepsy. Anthony Hopkins SSGC, editor. Chapmann and Hall, 1995: 269-281.

Triantafyllou N., Zalonis I., Kokotis P., Anthracopoulos M., Siafacas A., Malliara S., Hamburguer H.L., Papageorgiou C. Cognition in epilepsy: a multichannel event related potential (P300) study. Acta neurologica Scandinavica 1992; 86: 462-465.

Tuunainen A., Nousiainen U., Pilke A., Mervaala E., Riekkinen P. Lateralization of event-related potentials during discontinuation of anti-epileptic medication. Epilepsia 1995; 36: 262-269.

Vaz Pato M., Jones S.J. Cortical processing of complex tone stimuli: mismatch negativity at the end of a period of rapid pitch modulation. Cognitive Brain Research 1999; 7: 295-306.

Vaz Pato M., Jones S.J., Perez N., Sprague L. Mismatch negativity to single and multiple pitch-deviant tones in regular and pseudo-random complex tone sequences. Clinical Neurophysiology. 2002 ;113(4):519-527.

Velasco M., Velasco F.O. Subcortical correlates of the somatic auditory and visual vertex activities.II. Referential EEG responses. Electroencephalography and clinical Neurophysiology 1986; 63: 62-67.

Velasco M., Velasco F.O., Olvera A. Subcortical correlates of the somatic, auditory and visual vertex activities in man. I. Bipolar EEG responses and electrical stimulation. Electroencephalography and clinical Neurophysiology 1985; 61: 519-529.

Verkindt C., Bertrand O., Perrin F., Echallier J.-F., Pernier J. Tonotopic organization of the human auditory cortex : N100 topography and multiple dipole analysis. Electroencephalography and clinical Neurophysiology 1995; 96: 143-156.

Verleger R., Heide W., Butt C., Kompf D. Reduction of P3b in patients with temporo-parietal lesions. Brain Research. Cognitive Brain Research 1994; 2: 103-116.

Verleger R., Lefebre C., Wieschemeyer R., Kompf D. Event-related potentials suggest slowing of brain processes in generalised epilepsy and alterations of visual processing in patients with partial seizures. Brain Research. Cognitive Brain Research 1997; 5: 205-219.

Warrington E.P. Recognition Memory Test manual. Windsor: 1984.

Wallace M.N., Johnston P.W., Palmer A.R. Histochemical identification of cortical areas in the auditory region of the human brain. Experimental Brain Research. 2002 143(4): 499-508.

Webster W.R., Garey L.J. Auditory system. In: The human nervous system. Academic Press, 1990: 889-941.

Whitfield I.C. Auditory cortex and the pitch of complex tones. Journal of the Acoustical Society of America 1980; 67: 644-647.

Whitfield I.C. The role of auditory cortex in behaviour. In: Cerebral cortex. Association and auditory cortices. A.Peters and E.G.Jones, editor. Plenum, 1985: 329-349.

Whitfield I.C., Evans E.F. Responses of auditory cortical neurons to stimuli of changing frequency. Journal of Neurophysiology 1965; 28: 655-672.

Wieser H-G. Behavioural consequences of temporal lobe resection. In: The temporal lobes and the limbic system. M.R.Trimble T.G.B., editor. Wrightson Biomedical Publishing Ltd, 1992: 169-188.

Wieser H-G. Selective amygdalohippocampectomy. In: Surgical treatment of epilepsies. Jerome Engel, editor. Philadelphia: Lipincott Raven, 1994, 155-170.

Winkler I., Czigler I. Mismatch negativity: Deviance detection or the maintenance of the 'standard'. Neuroreport 1998; 9 (17): 3809-3813.

Winkler I., Reinikainen K., Näätanen R. Event-related brain potentials reflect traces of echoic memory in humans. Perception & Psychophysics 1993; 53: 443-449.

Winkler I., Schröger E., Cowan N. The role of large-scale memory organization in the mismatch negativity event-related brain potential. Journal of Cognitive Neurosciences 2001; 13: 59-71.

Wolff C., Schroger E. Activation of the auditory pre-attentive change detection system by tone repetitions with fast stimulation rate. Brain Research. Cognitive Brain Research 2001: 10 (3): 323-327.

Wolpaw J.R., Penry J.K. A temporal component of the auditory response. Electroencephalography and clinical Neurophysiology, 39: 609-620.

Woods D.L., Clayworth C.C., Knight R.T., Simpson G.V., Naeser N.A. Generators of middle and long latency auditory evoked potentials: implications from studies of patients with bitemporal lesions. Electroencephalography and clinical Neurophysiology 1987; 68: 132-148.

Woods D.L., Knight R.T., Neville H.J. Bitemporal lesions dissociate auditory evoked potencials and perception. Electroencephalography and clinical Neurophysiology, 1984; 57: 208-220.

Woods D.L., Knight R.T., Scabini D. Anatomical substracts of auditory selective attention: behavioural and electrophysiological effects of posterior association cortex lesions. Brain Research. Cognitive Brain Research 1993; 1: 227-240.

Yabe H., Tervaniemi M., Reinikainen K., Näätanen R. Temporal window of integration revealed by MMN to sound omission. Neuroreport 1997; 8 (8): 1971 -1974.

Yabe H., Winkler I., Czigler I., Koyama S., Kakigi R., Sutoh T., Hiruma T., Kaneko S. Organizing sound sequences in the human brain: the interplay of auditory streaming and temporal integration. Brain Research. 2001; 897: 222-227.

Young E.D., Brownell W.E. Responses to tones and noise of single cells in the dorsal cochlear nucleus of unanesthetized cats. Journal of Neurophysiology 1976; 39: 282-300.

Zatorre R.J., Evans A.C., Meyer E. Neural mechanisms underlying melodic perception and memory for pitch. Journal of Neuroscience 1994; 14: 1908-1919.

Zatorre R.J., Samson S. Role of the right temporal neocortex in retention of pitch in auditory short-term memory. Brain 1991; 114: 2403-2417.

Zatorre R.J. Pitch perception of complex tones and human temporal lobe function. Journal of the Acoustical Society of America 1988; 84: 566-572.

Appendix

Normal control subjects - tables of mean values and S.D. for amplitude and latency

Amplitude values

Table 6-1 Mean and S.D. of the amplitude values for 31 normal subjects (Onset).

Onset (μV)		Mean ON1	S.D.	Mean OP2	S.D.
Midline	Nose	-2.6	2.4	0.6	1.5
	Fz	-6.7	2.9	4.5	2.1
	Cz	-6.1	2.7	5.5	2.4
	Pz	-3.8	2.0	2.8	1.7
Right	Fp2	-4.4	3.0	2.3	1.8
	F4	-6.2	3.0	4.6	1.9
	F8	-3.5	2.8	1.6	1.8
	C4	-5.0	2.3	4.1	2.0
	T4	-1.9	2.7	0.4	1.9
	T6	-0.8	1.5	0.3	1.5
Left	Fp1	-4.5	2.6	2.1	1.7
	F3	-5.9	2.7	4.6	1.7
	F7	-3.2	2.3	1.2	1.8
	C3	-5.5	2.1	4.2	1.9
	T3	-1.6	2.3	0.2	1.9
	T5	-0.9	1.8	0.04	1.2

Table 6-2. Mean and S.D. of the amplitude values for 31 normal subjects (Frequency Change).

Frequency Change (μV)		Mean CN1	S.D.	Mean CP2	S.D.
Midline	Nose	-2.1	2.3	2.0	1.3
	Fz	-6.6	3.3	3.1	7.8
	Cz	-7.4	3.4	3.8	9.3
	Pz	-4.0	2.2	2.1	4.5
Right	Fp2	-4.1	2.8	2.9	4.2
	F4	-6.9	3.3	3.3	7.3

	F8	-3.8	3.1	2.8	2.9
	C4	-5.5	2.9	2.4	5.9
	T4	-1.7	2.5	2.1	.67
	T6	-0.5	1.8	1.5	.02
Left	Fp1	-4.3	2.8	2.8	4.1
	F3	-6.5	3.0	3.3	6.9
	F7	-2.9	2.4	2.3	2.0
	C3	-5.7	3.1	3.1	5.9
	T3	-1.8	2.5	2.2	0.4
	T5	-0.7	1.7	1.3	0.3

Table 6-3. Mean and S.D. of the amplitude values for 31 normal subjects (Mismatch).

Mismatch (μV)		**Mean MN1**	**SD**	**Mean MP2**	**SD**
Midline	Nose	1.5	-3.1	2.2	1.8
	Fz	2.5	-6.2	5.5	2.7
	Cz	2.3	-5.3	4.8	2.4
	Pz	1.6	-2.7	2.2	1.3
Right	Fp2	2.5	-4.1	4.2	2.8
	F4	2.6	-5.9	5.7	2.6
	F8	1.8	-4.0	2.3	2.0
	C4	2.3	-4.4	3.4	2.3
	T4	2.2	-1.9	0.7	2.1
	T6	1.7	-0.7	0.2	1.2
Left	Fp1	2.8	-4.7	3.8	2.8
	F3	2.6	-5.8	4.7	2.4
	F7	1.9	-3.3	1.8	2.0
	C3	2.5	-4.3	3.4	2.2
	T3	1.5	-1.4	0.0	1.5
	T5	1.4	-0.5	0.5	0.9

Table 6-4. Mean, S.D. and normal limits for amplitude ratio between the right and left electrodes (Onset).

Ratio =(F4-F3)/(F4+F3)	**Mean**	**S.D.**
ON1	0.01	0.18
OP2	0.00	0.16
	Minimum	**Maximum**
ON1	-0.45	0.47
OP2	-0.40	0.40
Ratio=(C4-C3)/(C4+C3)	**Mean**	**S.D.**
ON1	-0.06	0.17
OP2	-0.03	0.28
	Minimum	**Maximum**
ON1	-0.48	0.37
OP2	-0.74	0.68

Table 6-5. Limits for amplitude after logarithm transformation (Onset).

Onset (μV)		**Min ON1**	**Max ON1**	**Min O P2**	**Max OP2**
Midline	Nose				
	Fz	-1.8	-19.2	0.8	18.7
	Cz	-1.9	-19.2	1.3	19.2
	Pz	-0.7	-15.8	0.2	22.9
Right	Fp2				
	F4	-1.2	-23.9	1.4	12.5
	F8				
	C4	-1.3	-15.6	0.5	23.4
	T4				
	T6				
Left	Fp1				
	F3	-1.4	-19.3	1.6	11.5
	F7				
	C3	-1.7	-14.8	1.0	14.5

	T3				
	T5				

Table 6-6 Mean, S.D. and normal limits for amplitude ratio between the right and left electrodes (Frequency Change).

Ratio = (F4-F3)/(F4+F3)	**Mean**	**S.D.**
CN1	0.03	0.12
CP2	0.03	0.17
	MINIMUM	**MAXIMUM**
CN1	-0.26	0.33
CP2	-0.39	0.44
Ratio = (C4-C3)/(C4+C3)	**Mean**	**S.D.**
CN1	-0.02	0.17
CP2	0.03	0.22
	MINIMUM	**MAXIMUM**
CN1	-0.26	0.65
CP2	-0.40	0.61

Table 6-7 Amplitude limits after logarithm transformation (Frequency Change).

Frequency Change (μV)		**Min CN1**	**Max CN1**	**Min CP2**	**Max CP2**
Midline	Nose				
	Fz	-1.6	-21.5	2.8	18.3
	Cz	-1.6	-25.8	3.2	22.9
	Pz	-0.7	-16.4	1.1	14.5
Right	Fp2				
	F4	-1.6	-22.6	1.9	22.6
	F8				
	C4	-1.3	-18.0	1.7	16.9
	T4				
	T6				
Left	Fp1				

	F3	-1.6	-20.6	1.8	21.5
	F7				
	C3	-1.1	-25.0	1.1	23.2
	T3				
	T5				

Table 6-8 Amplitude limits (Mismatch).

Mismatch (μV)		**MIN MN1**	**MAX MN1**	**MIN MP2**	**MAX MP2**
Midline	Nose				
	Fz	-2.0	-16.1	1.2	19.4
	Cz	-1.5	-15.3	1.2	14.8
	Pz	-0.5	-11.4	0.6	7.1
Right	Fp2				
	F4	-1.9	-15.7	1.2	20.5
	F8				
	C4	-1.0	-14.8	0.7	15.5
	T4				
	T6				
Left	Fp1				
	F3	-1.6	-17.4	0.8	19.8
	F7				
	C3	-1.0	-15.8	0.6	13.2
	T3				
	T5				

Table 6-9. Mean, S.D. and normal limits for amplitude ratio between the right and left electrodes (Mismatch)

.Ratio = (F4-F3)/(F4+F3)	**Mean**	**S.D.**
MN1	0.01	0.14
MP2	0.11	0.17

	Minimum	Maximum
MN1	-0.34	0.36
MP2	-0.32	0.54
Ratio = (C4-C3)/(C4+C3)	**Mean**	**S.D.**
MN1	0.01	0.24
MP2	0.00	0.24
	Minimum	**Maximum**
MN1	-0.59	0.61
MP2	-0.60	0.60

Latency values

Table 6-10. Mean and S.D.of the latency values for 31 normal subjects (Onset).

ON1 (ms)	**Mean**	**S.D.**
Midline Fz	84.4	7.3
Right F4	84.2	7.3
Left F3	83.9	7.2
OP2	**Mean**	**S.D.**
Midline Fz	155.0	8.5
Right F4	157.1	10.6
Left F3	154.0	9.9

Table 6-11. Mean and S.D. of the latency values for 31 normal subjects (Frequency Change).

CN1 (ms)	**Mean**	**S.D.**
Midline Fz	85.8	8.7
Right F4	86.1	9.4
Left F3	85.6	7.4
CP2	**Mean**	**S.D.**
Midline Fz	160.1	8.8

Right F4	160.9	9.6
Left F3	158.9	11.0

Table 6-12. Mean and S.D. of the latency values for 31 normal subjects (Mismatch).

MN1 (ms)	**Mean**	**S.D.**
Midline-Fz	97.0	11.4
Right-F4	97.2	11.4
Left-F3	95.5	11.3
MP2	**Mean**	**S.D.**
Midline-Fz	180.9	10.9
Right-F4	182.7	14.5
Left-F3	183.2	16.0

Table 6-13 Latency normal limits for ON1/OP2 complex (mean $\pm$ 2.5 S.D.) (Onset).

ON1(ms)	**MINIMUM**	**MAXIMUM**
Midline Fz	66.2	102.6
Right F4	66.0	102.5
Left F3	65.9	101.9
OP2		
Midline Fz	133.8	176.3
Right F4	130.6	183.6
Left F3	129.2	178.8

Table 6-14. Mean, S.D.and limits for latency differences between right and left electrodes (Onset).

Onset (ms)	**Mean ON1**	**S.D.**	**Mean OP2**	**S.D.**
R-L (F4-F3)	0.3	3.1	3.0	8.7
	Min ON1	**Max ON1**	**Min OP2**	**Max OP2**
R-L (F4-F3)	-7.3	7.9	-18.7	24.8

Table 6-15. Normal limits for latency for CN1/CP2 complex (mean ± 2.5 S.D.) (Frequency Change).

CN1 (ms)	**Minimum**	**Maximum**
Midline Fz	64.1	107.6
Right F4	62.6	109.6
Left F3	67.1	104.1
CP2		
Midline Fz	138.1	182.1
Right F4	136.9	184.9
Left F3	131.4	186.4

Table 6-16. Latency differences between right and left electrodes (Frequency Change).

Frequency Change (ms)	**Mean CN1**	**SD**	**Mean CP2**	**SD**
R-L (F4-F3)	0.5	4.1	2.0	10.9
	Min CN1	**Max CN1**	**Min CP2**	**Max CP2**
R-L (F4-F3)	-9.8	10.8	-25.2	29.2

Table 6-17. Normal limits for latency for MN1/MP2 complex (mean ± 2.5 S.D.)

MN1 (ms)	**Minimum**	**Maximum**
Midline Fz	68.5	125.5
Right F4	68.7	125.7
Left F3	67.2	123.8
MP2	**Minimum**	**Maximum**
Midline Fz	154.7	209.2
Right F4	146.5	219.0
Left F3	143.2	223.2

Table 6-18. Latency differences between right and left electrodes (Mismatch).

Mismatch (ms)	**mean MN1**	**S.D.**	**mean MP2**	**S.D.**
R-L (F4-F3)	1.7	7.3	-0.5	6.9
	Min MN1	**Max MN1**	**Min MP2**	**Max MP2**

R-L (F4-F3)	-16.7	20.0	-17.8	16.9

Table 6-19: Number of positive and negative responses for latency and amplitude difference.

	Latency N1 (xr-xl)		Latency P2 (xr-xl)		Amplitude N1 (xr-xl)/(xr+xl)		Amplitude P2 (xr-xl)/(xr+xl)	
	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.	Pos.	Neg.
Onset	24	7	22	9	11	20	15	16
F. Change	18	13	22	9	14	17	16	15
Mismatch	23	8	22	9	15	16	18	13

The T- complex

Table 6-20. Latency of the Onset condition (T-complex).

Onset (ms)	**Mean**	**S.D.**
Ta (T4)	141.7	18.1
Tb (T4)	201.1	23.8
Ta (T3)	146.0	16.0
Tb (T3)	199.1	30.9

Table 6-21. Normal values for R-L latency differences-Onset (T-complex).

Onset R-L difference (ms)	**Mean**	**S.D.**
Ta	-3.4	15.5
Tb.	-0.2	34.4

Table 6-22. Latency of the Frequency Change condition (T-complex)

Frequency Change (ms)	**Mean**	**S.D.**	**Minimum**	**Maximum**
Ta (T4)	143.4	17.2	100.5	186.3

Tb (T4)	203.3	21.6	149.3	257.3
Ta (T3)	142.3	17.8		
Tb (T3)	202.1	36.9		

Table 6-23. Normal values for R-L latency differences-Onset (T-complex).

F. Change R-L difference (ms)	**Mean**	**S.D.**
Ta	**0.27**	**21.27**
Tb.	**-0.58**	**32.28**

Test/retest variability in normal controls

Onset test/retest values for normal controls

Table 6-24: Latency values for the first (1) and second (2) recordings. Latency values were measured from F4 (right) and F3 (left) (Onset).

Onset (ms)	First recording		Second recording	
	Mean	S.D.	Mean	S.D.
ON1R	84.1	8.8	86.0	9.2
ON1L	84.8	8.6	86.2	8.7
OP2R	160.0	12.0	161.1	13.3
OP2L	161.4	9.5	159.6	13.7

Table 6-25 Latency differences between the first and second recordings (Onset).

Onset (ms) (x1-x2)	MEAN	S.D.
ON1R	1.1	8.2
ON1L	-1.4	5.1
OP2R	2.7	11.2
OP2L	5.7	11.5

Table 6-26: Normal limits for latency differences between the first and second recordings (mean ± S.D.).

Onset (ms)	Minimum	Maximum
ON1R	-19.5	21.6
ON1L	-14.1	11.3
OP2R	-25.4	30.8
OP2L	-23.0	34.6

Table 6-27. Mean and S.D.. amplitude values (N1, P2) for the first (1) and second (2) recordings (Onset).

Onset (μV)	First recording		Second recording	
	Mean	S.D.	Mean	S.D.
ON1R (F4)	-6.7	2.8	-6.0	2.7
ON1L (F3)	-5.8	2.7	-6.0	2.3

OP2R (F4)	3.7	1.8	4.0	2.7
OP2L (F3)	3.8	1.7	3.2	1.9
ON1R (C4)	-5.3	2.3	-4.6	2.2
ON1L (C3)	-5.5	2.1	-4.3	2.1
OP2R (C4)	3.2	1.8	3.9	2.0
OP2L (C3)	3.7	1.6	3.0	2.0

Table 6-28: Mean and S.D. of amplitude ratio between the first and second measurements (Onset).

Ratio= (Fx(1)-Fx(2))/(Fx(1)+Fx(2))	**Mean**	**S.D.**
Right ON1(F4)	0.05	0.22
Left ON1 (F3)	0.01	0.21
Right OP2 (F4)	-0.08	0.29
Left OP2 (F3)	0.11	0.33
Ratio= (Cx(1)-Cx(2))/(Cx(1)+Cx(2))	**Mean**	**S.D.**
Right ON1(C4)	0.07	0.25
Left ON1 (C3)	0.12	0.29
Right OP2 (C4)	-0.08	0.31
Left OP2 (C3)	0.06	0.31

Table 6-29. Normal limits (amplitude ratio) between the first and second measurements (Onset)

Ratio= (Fx(1)-Fx(2))/(Fx(1)+Fx(2))	**Minimum**	**Maximum**
Right ON1	-0.50	0.60
Left ON1	-0.52	0.54
Right OP2	-0.81	0.65
Left OP2	-0.72	0.94
Ratio= (Cx(1)-Cx(2))/ (Cx(1)+Cx(2))	**Minimum**	**Maximum**
Right ON1	-0.56	0.70
Left ON1	-0.61	0.85
Right OP2	-0.86	0.70
Left OP2	-0.72	0.78

Table 6-30: Latency values for the first (1) and second (2) recordings. Latency values were measured from F4 (right) and F3 (left) (Onset).

Onset (ms)	First recording		Second recording	
	Mean	S.D.	Mean	S.D.
ON1R	84.1	8.8	86.0	9.2
ON1L	84.8	8.6	86.2	8.7
OP2R	160.0	12.0	161.1	13.3
OP2L	161.4	9.5	159.6	13.7

Frequency Change test/retest values for normal controls

Table 6-31: Latency values for the first (1) and second (2) recordings. Latency values were measured from F4 (right) and F3 (left) (Frequency Change)

Onset (ms)	First recording		Second recording	
	Mean	S.D.	Mean	S.D.
CN1R	89.0	9.8	85.8	8.3
CN1L	86.3	9.3	84.7	7.3
CP2R	170.2	16.3	165.1	8.3
CP2L	167.0	10.6	158.7	8.3

Table 6-32. Latency differences between the first and second recordings. (Frequency Change).

Frequency Change (ms)	Mean	S.D.
CN1R	3.3	8.5
CN1L	1.5	6.2
CP2R	5.1	13.3
CP2L	8.3	13.2

Table 6-33. Normal limits for latency differences between first and second recordings (mean $\pm$ S.D.) (Frequency Change)

	Minimum	Maximum
Right CN1	-18.1	24.6
Left CN1	-14.0	17.1

Right CP2	-28.2	38.5
Left CP2	-24.8	41.4

Table 6-34. Mean and S.D. of CN1 and CP2 amplitudes for the first and second recordings (Frequency Change).

Fr.Change (μV)	**First recording**		**Second recording**	
	Mean	**SD**	**Mean**	**SD**
CN1R (F4)	-5.9	3.1	-5.7	4.1
CN1L (F3)	-6.0	2.9	-5.5	3.6
CP2R (F4)	7.4	2.8	7.1	4.1
CP2L (F3)	6.4	3.2	7.3	4.1
CN1R (C4)	-4.8	2.7	-4.6	3.1
CN1L (C3)	-5.4	2.4	-4.4	2.7
CP2R (C4)	6.2	2.1	6.4	3.6
CP2L (C3)	6.1	2.5	6.4	4.1

Table 6-35. Mean and S.D. of amplitude ratio between the first and second measurements (Frequency Change).

Ratio=(Fx1-Fx2)/(Fx1+Fx2)	**Mean**	**S.D.**
Right CN1	0.08	0.34
Left CN1	0.09	0.27
Right CP2	0.04	0.18
Left CP2	-0.04	0.34
Ratio=(Cx1-Cx2)/(Cx1+Cx2)	**Mean**	**S.D.**
Right CN1	0.01	0.28
Left CN1	0.03	0.24
Right CP2	0.11	0.30
Left CP2	0.05	0.26

Table 6-36. Limits for amplitude ratio for both pairs of electrodes F4, F3 and C4,C3 (Frequency Change).

Ratio =(F4-F3)/(F4+F3)	**Minimum**	**Maximum**
Right CN1	-0.77	0.93

Left CN1	-0.59	0.77
Right CP2	-0.41	0.49
Left CP2	-0.89	0.81
Ratio=(C4-C3)/(C4+C3)	**Minimum**	**Maximum**
Right CN1	-0.69	0.71
Left CN1	-0.57	0.63
Right CP2	-0.64	0.86
Left CP2	-0.60	0.70

Mismatch test/retest values for normal controls

Table 6-37. Mean and S.D. of MN1 and MP2 amplitudes for the first and second recordings (Mismatch)

Mismatch (μV)	**First recording**		**Second recording**	
	Mean	**SD**	**Mean**	**SD**
MN1R (F4)	95.7	8.1	95.2	9.2
MN1L (F3)	95.7	8.0	95.0	10.0
MP2R (F4)	181.4	11.9	181.0	6.8
MP2L (F3)	179.3	10.5	183.1	27.7

Table 6-38. Latency difference between the first and second measurements (Mismatch).

Mismatch (ms)	**Mean**	**S.D.**
Right MN1	0.6	8.4
Left MN1	0.3	12.0
Right MP2	0.8	9.3
Left MP2	2.3	9.0

Table 6-39. Normal limits for latency difference between first and second measurements (Mismatch)

Mismatch (ms)	**Minimum**	**Maximum**
Right MN1	-20.5	21.7
Left MN1	-29.6	30.3

Right MP2	-22.6	24.1
Left MP2	-20.2	24.7

Table 6-40. Mean and S.D. (MN1 and MP2) for the first (1) and second (2) recordings

Mismatch (μV)	**Mean MN1**	**SD**	**Mean MP2**	**SD**
Right (F4)-1	-5.1	3.2	6.1	2.7
Left (F3)-1	-5.1	2.0	5.9	2.8
Right (F4)-2	-6.0	2.2	6.4	2.7
Left (F3)-2	-5.5	1.5	6.0	2.8
	Mean MN1	**SD**	**Mean MP2**	**SD**
Right (C4)-1	-4.0	3.0	4.3	1.9
Left (C3)-1	-4.2	1.8	4.3	2.7
Right (C4)-2	-5.1	2.0	4.2	2.2
Left (C3)-2	-4.7	1.9	4.4	2.3

Table 6-41. Mean and S.D. of amplitude difference ratio between the first and second recordings. Amplitude values were measured from F4 and C4 (right) and F3 and C3 (left) electrodes (Mismatch).

Ratio = (Fx1-Fx2)/(Fx1+Fx2)	**Mean**	**S. D.**
Right MN1	-0.17	0.32
Left MN1	-0.08	0.26
Right MP2	0.01	0.26
Left MP2	0.01	0.29
Ratio = (Cx1-Cx2)/(Cx1+Cx2)	**Mean**	**S.D.**
Right MN1	-0.18	0.31
Left MN1	-0.08	0.25
Right MP2	0.01	0.26
Left MP2	0.01	0.29

Table 6-42. Normal limits for the amplitude ratio (Mismatch).

Ratio=(Fx1-Fx2)/(Fx1+Fx2)	**Minimum**	**Maximum**
Right MN1	-0.92	0.58

Left MN1	-0.83	0.67
Right MP2	-0.74	0.76
Left MP2	-0.74	0.76
Ratio=(Cx1-Cx2)/(Cx1+Cx2)	**Minimum**	**Maximum**
Right MN1	-0.96	0.60
Left MN1	-0.71	0.55
Right MP2	-0.64	0.66
Left MP2	-0.72	0.74

Table 6-43. Normal latency values for repeated test/retest -Onset (T-complex)

Onset (X1-X2) (ms)	**Mean**	**S.D.**
Ta R (Ta1-Ta2)	-7.3	16.8
Tb R (Tb1-Tb2)	5.9	27.9
Ta L (Ta1-Ta2)	-12.1	7.0
Tb L (Tb1-Tb2)	-11.3	26.6

Table 6-44. Normal values for R-L latency differences- Frequency Change (T-complex).

Frequency change R-L difference (ms)	**Mean**	**S.D.**	**Minimum**	**Maximum**
Ta (Ta1-Ta2)	0.3	21.3	-52.9	53.5
Tb (Tb1-Tb2)	-0.6	32.3	-81.3	80.1

Table 6-45. Normal latency values for repeated test/retest- Frequency Change (T-complex)

Frequency change (x1-x2) (ms)	**Mean**	**S.D.**	**Minimum**	**Maximum**
Ta R	-12.0	29.1	-84.8	60.8
Tb R	-15.6	41.3	-118.7	87.5
Ta L	6.0	7.4		
Tb L	21.00	44.0		